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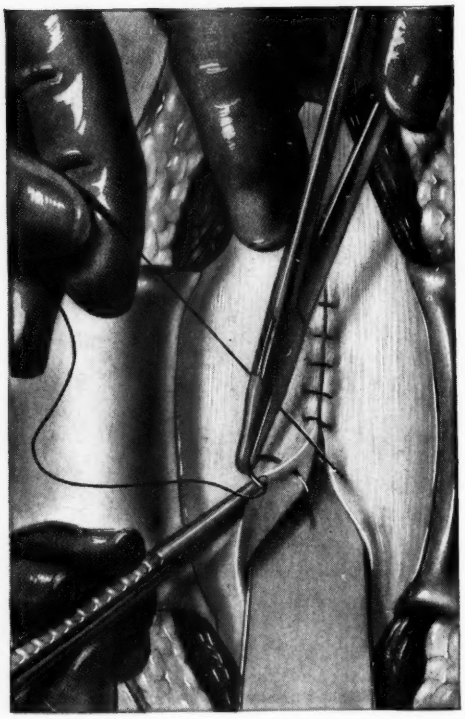
With International Abstracts of Surgery

VOLUME 96 May, 1953 NUMBER 5



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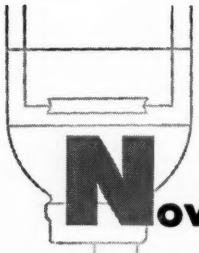

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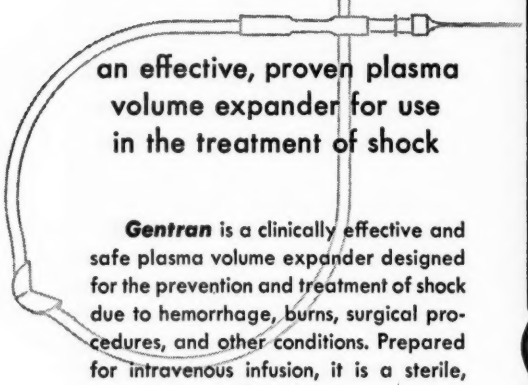

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SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 96 MAY, 1953 NUMBER 5

THE ARGUMENT FOR PREOPERATIVE RADIATION IN THE TREATMENT OF BREAST CANCER

C. L. ASH, M.D., VERA PETERS, M.D., and NORMAN C. DELARUE, M.D.,
Toronto, Canada

As gradual control is effected against the primary killing diseases of the last century, the death rate from pneumonia, tuberculosis, infections, and parasites continues to fall steadily, with the result that the mortality due to heart disease and cancer, the two major disease processes as yet uncontrolled, shows a progressive increment.

Although in males cancer never becomes the commonest cause of death in any age group, it does claim that position in the mortality statistics of women between the ages of 30 and 60 years, and approximates very closely the death rate from cardiovascular disease between 60 and 75 years of age, this prevalence being due in significant proportion to the incidence of carcinoma of the breast at these ages. In the total white population, skin cancer leads in incidence per 100,000 population (33), with breast cancer in second place (29), but in women alone the breast lesion shows an incidence of 56 victims per 100,000 population, as compared with the skin cancer incidence rate of 28. This disease then becomes one of the most important problems of our era.

Following the acceptance of the radical operation of Halsted as the surgical treatment of choice, it was generally believed that a radical mastectomy was one of the most adequate methods available in extirpating cancer anywhere in the body, with wide removal of the local lesion, coupled with an anatomic dissection of the accessible lymphatic drainage fields. Undoubtedly the immediate result was much improved, with a local recurrence rate in skilled hands of approximately 10 to 30 per cent as compared with the results of simple mastectomy, in which local recurrences appeared in 62 to 82 per cent of cases. The problem of treatment of carcinoma of the breast then became standardized, with the exception of minor arguments only concerning the advisability of wide or limited skin excision, the use of thick or thin skin flaps, and finally the value of radiotherapy as an adjunct to surgical treatment.

However, a closer appraisal of the end results obtained by this method of treatment led critical observers to question the validity of these opinions, when the following causes for dissatisfaction became apparent.

In the first place, although inherent biologic differences have long been observed in the growth of breast tumors, with some patients harboring lesions frequently of large size for 10 to 20 years, and occasionally longer, whereas others with relatively small lesions succumb to their disease in a very few months, none-

From the Ontario Institute of Radiotherapy and the Department of Surgery, Toronto General Hospital, Toronto, Canada.

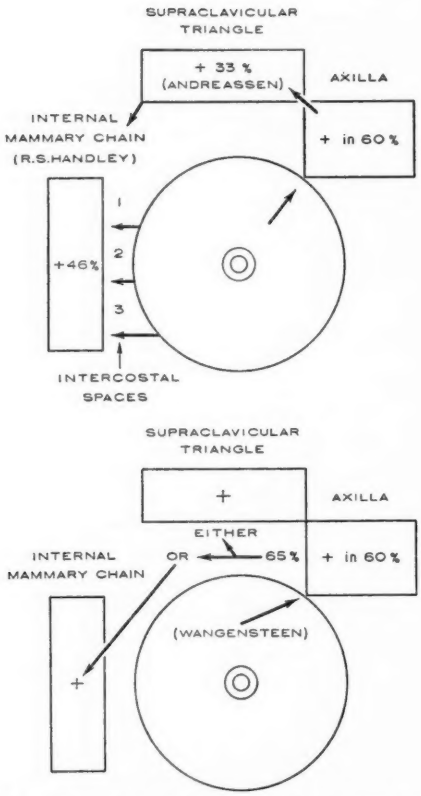

Fig. 1. Lymph node involvement in mammary carcinoma. Cases thought suitable for radical mastectomy.

theless the mean survival period in untreated cases has been reported to be well over 3 years, and the 5 year survival figure for untreated cases varies somewhere between 19 and 22 per cent. When one compared these figures with the results of radical surgical treatment at highly specialized centers, and found the survival rate only 33 per cent (collected data, circa 1930 to 1940) even in a selected group of cases thought suitable for operation, it was difficult to become enthusiastic advocates of the value of the radical procedure. In addition, approximately 60 per cent of patients chosen for radical mastectomy were found to have involved axillary nodes, with a fall in the 5 year survival from 70 per cent in the stage I cases to 30 per cent or lower in this larger group. These statistics of axillary nodal involvement were almost constant throughout the larger centers reporting on this problem (Presbyterian Hospital 61.6 per cent (6); Toronto General Hospital 63.4 per cent), and represented the fundamental basis for stressing originally the value of early diagnosis. More recently, careful analyses, particularly in a few larger American centers, of the end results obtained in certain advanced or complicated types of the disease showed a complete failure to produce 5 year survivals by surgical treatment, and these patients were grouped together as "categorically inoperable," indicating that they were no longer being considered as surgical problems at all.

Along purely statistical lines it has been pointed out that there has been no fall in the death rate due to carcinoma of the breast in the general population, whereas surely if the present treatment of the disease was of any value it should result in an appreciable reduction in the number of deaths due to the disease treated. According to McKinnon, this failure to influence the death rate due to carcinoma of the breast is demonstrated in a study of age-specific death rates and is not due to the fact that more people are living in the cancer age group. This observation, however, is for several reasons not thought to be as significant as it would appear on the surface. In the first place, there can be no doubt that the diagnosis of breast cancer has been improved both in the medical and lay population, so that an appreciably greater number of cases will be seen as compared with the statistics of older vintage. Unfortunately too, once the patient has suffered from an authenticated carcinoma of the breast, the subsequent death is all too frequently noted on the death certificate as being due to this disease when an entirely different and unrelated pathologic process has caused the fatal termination. This well known inaccuracy of death certification has recenlly been stressed by Public Health officials and clinicians alike. With these two major factors in mind, it is encouraging that the death rate is being at least maintained at a stable level, and we think that it does, in fact, indicate that treatment is effective in improving the survival rate

in patients treated. Certainly the authors who have drawn attention to these facts do not suggest that the patient with breast cancer should not be treated, but merely desire to stimulate a more thoughtful and analytic approach to a problem which is far from solution as yet. The psychologic effect alone of making the attempt to rid a patient of her disease demands that clinical treatment of some kind be given.

At any rate, it was the natural outcome of these observations that an attempt should be made to determine the reasons why patients continue to die, regardless of the radical nature of the surgical procedure. Obviously their deaths from the disease could only mean that metastases are present beyond the limits of the anatomic dissection, these metastases having been already present preoperatively or having resulted from the surgical procedure. The following factors appear significant in the further appraisal of this supposition:

1. Lymphatic deposits can be demonstrated in nodal areas other than those included in the operative field. According to R. S. Handley (9, 10) (Fig. 1) 46 per cent of patients with axillary nodal involvement (approximately 60 per cent of the total) will have deposits in the internal mammary chain, and 33 per cent will show metastases in the supraclavicular area, as reported by Andreassen. Wangensteen (25) summarizes these statistics by stating that 65 per cent of these patients with axillary involvement will show either supraclavicular or internal mammary nodal extension. Both these zones are, of course, beyond the scope of the usual surgical operation as practiced today. It is interesting to note also that Handley (9, 10) (Fig. 2) has found that 11 per cent of patients having no demonstrable axillary nodal involvement nonetheless show metastases in the internal mammary chain, and that 60 per cent of inner quadrant lesions (20 per cent for lesions in the outer quadrant) have spread to the anterior mediastinum when treatment is carried out. Because of the limited dissection of the internal mammary chain made in determining these figures, they represent unfortunately the minimum involvement, and it is quite possible that the figure is in reality considerably higher.

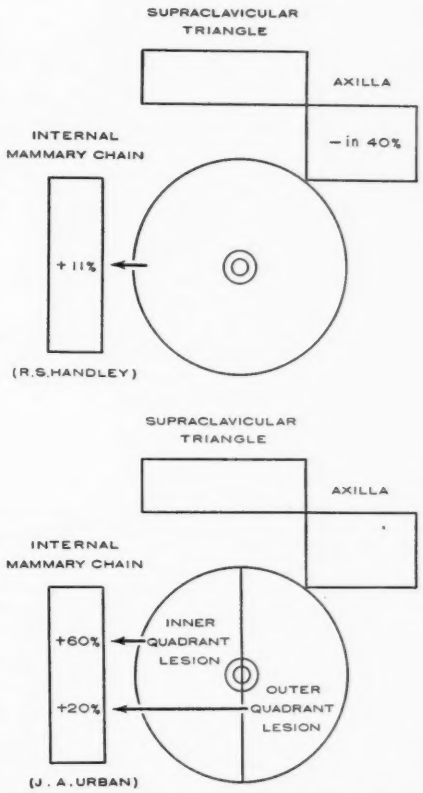

Fig. 2. Mammary carcinoma. Further statistics regarding internal mammary node involvement.

Because of the infrequency with which residual disease is subsequently recognized in the anterior mediastinum, it is interesting to speculate concerning the clinical significance of this high rate of involvement in the internal mammary nodes. Certainly metastatic disease in this region alone cannot often represent the cause of death, although further distant dissemination from the site of secondary involvement may result in metastases to vital organs by way of lymphatic or hematogenous channels. Consequently treatment should be directed to this area if possible, in any rational attempt to improve the survival rate.

2. It was originally taught by the elder Handley (11) that breast carcinomas spread only by means of lymphatic permeation, and

although it has been appreciated for some time that lymphatic embolism undoubtedly occurs also, it was not until more recently that the possibility of hematogenous metastases was generally accepted. Following Batson's demonstration of the peculiarly valveless system of veins that permeate the spinal axis from skull to pelvis, and the statistical evidence of the preponderance of bony metastases in these areas, there seems no reasonable doubt that spread by way of this venous plexus is quite common. The frequency, too, of pulmonary deposits points in addition to a hematogenous origin that cannot be denied.

Whether or not secondary hematogenous involvement of these two types has already occurred by the time clinical recognition of the disease is made and treatment instituted is a difficult problem to assess, and has led recently to much clinical argument. On purely theoretic grounds, Park and Lees have felt that the tumor has been present for many years before the onset of symptoms, and further argue that delay in treatment has not been demonstrated to affect the 5 year survival. Whereas they estimate that 60 per cent of patients with a proved diagnosis of carcinoma of the breast have microscopically detectable axillary metastases at the time of onset of symptoms, it is reasonable to presuppose that the presence of the metastases was responsible in part for the patient seeking advice, and consequently theorizing on a different premise Gilliam suggests that it is possible, with a minimum increment of metastases following the onset, that no more than 11 per cent would have axillary involvement during the first month after symptoms develop. In all probability, the true figure lies somewhere between this minimum estimate and Park and Lees' figure which denotes a maximum degree of involvement. In favor of the more modest assumption, the University of California group (19) have recently demonstrated that with an apparent delay of less than 1 month between the onset of symptoms and the initial medical appraisal only 48 per cent of patients have such metastases, and the 5 year survival may be expected in this favorable group to be as high as 60 per cent because of the freedom from generalized or distant metastases. This figure is approximately 20 per cent higher than the actual 40 per cent survival in the entire group reported by them, and 40 per cent above the 20 per cent survival in untreated women.

Park and Lees also state that about 20 to 30 per cent of patients with a diagnosis of cancer of the breast do not develop axillary metastases within 3 years of the onset of symptoms, suggesting the lack of significant effect due to delay in treatment. There appears to be no doubt that, as Shimkin and his associates point out, the survival of patients following treatment in any specific stage of the disease has been shown to be independent of the apparent delay in initiating treatment. On the other hand, the ratio of stages changes with delay, and the process of staging tends to group women with neoplasms of different biologic properties, as outlined in Figure 3, so that those with the longest delay in any single stage will be biologically the least active. If the entire series is studied, however, there will be more stage I cases the earlier the diagnosis is made, and consequently a definite improvement in the results as noted previously. In our present state of knowledge then, it is preferable to continue to stress the importance of early diagnosis and treatment in an attempt to obtain the best results possible. It is readily admitted that further advances in the pretreatment determination of the biologic nature of the lesion present may alter these opinions and increase the accuracy with which cases are chosen for operation. There is no question but that the size of the tumor and the presence of metastases are, as Shimkim and his co-authors state, both functions of the length of time the tumor has been present as well as the biologic properties of the neoplasm.

3. Several authors have recently stressed the danger of axillary dissection during the performance of a typical radical mastectomy, insofar as it may spread the disease. It is generally accepted that division of a lymphatic channel blocked by carcinomatous permeation may release an embolus capable of initiating new disease elsewhere, and McWhirter (13) has made this danger the basis of the Edinburgh experiment in the treatment of breast

cancer, in which the axilla is left undisturbed, removing the primary lesion by simple mastectomy, and treating the nodal areas by postoperative radiotherapy. The possibility that this catastrophe may occur is accentuated by the fact that it is impossible accurately to delineate the extent of the disease preoperatively, or indeed at operation. In expert hands the clinical error in palpating axillary nodes varies between 30 and 55 per cent, and obviously at operation one cannot palpate the microscopically involved areas proved so common by such observers as Gatch, who believes that a true block dissection of an involved axilla is for this reason seldom if ever accomplished. Haagenson (7) has proved to his own satisfaction that gentleness and care in operative manipulation are essential, and he demonstrates a rising 5 year survival rate with the length of time taken to complete the operation. The pathologic demonstration of carcinoma cells on the surgeon's gloves or in the wash water of course may offer an explanation for some of the instances of local recurrences in the operative field or a donor area from which a skin graft has been taken.

With these three main factors responsible for postoperative deaths from the disease in mind, rational attacks on the problem have been made along several lines: (a) Most centers continue to stress the importance of early diagnosis, and we subscribe to this opinion for the reasons noted previously. (b) Halsted made the original surgical attack on the problem by attempting to excise all accessible areas of lymphatic permeation widely, including the axillary nodal area. There was dramatic improvement of the local recurrence rate as the result of this change from simple mastectomy. (c) As an extension of the attempt to rid the patient of lymphatic metastases, Wangensteen (23-25) has developed a "superradical operation" with removal of supraclavicular and internal mammary nodes in addition to the axillary field. A somewhat similar approach has been made by Urban, who dissects a portion of the internal mammary chain through a transcostal approach. Both these methods must await evaluation with the passage of time.

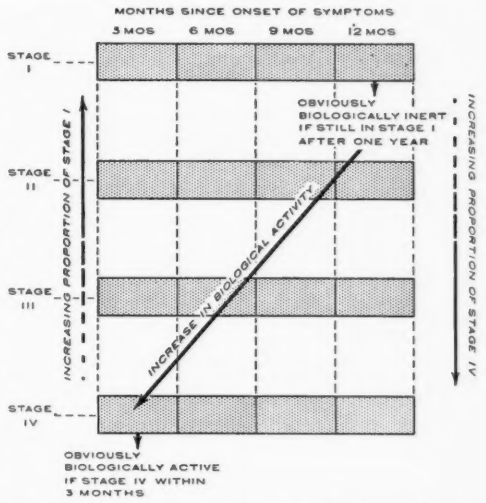

Fig. 3. Relation of stage of disease and delay in initiating treatment.

4. McWhirter (13), as outlined before, has been impressed by the danger of axillary dissection, and is following a group of cases treated by simple mastectomy with postoperative radiation. Although the 5 and 10 year survivals (14) by this method appear comparable in every way (Table IX) with the results of radical mastectomy, and the procedure has many obvious technical advantages as outlined below, we have not felt justified in using it for the reasons enumerated in the following tabulation:

RATIONALE OF SIMPLE MASTECTOMY

I. Danger of spread of cancer at time of axillary dissection minimized.
II. Technical simplicity of operation.
III. Negligible mortality rate.
IV. Considerable diminution in morbidity rate.
V. No appreciable limitation of shoulder motion.
VI. Swelling of arm almost unknown.

OBJECTIONS TO SIMPLE MASTECTOMY AS ELECTIVE FORM OF SURGICAL TREATMENT

I. Increased incidence of local recurrence results because of: (a) relatively limited skin removal; (b) skin flaps commonly thicker; (c) dissection of breast not carried out as widely as in radical mastectomy, with danger of leaving residual breast tissue; (d) failure to remove fascial plexus of lymphatic channels.

II. Sixty-five per cent of cases with axillary node involvement harbor residual disease since: (a) more than 60 per cent of cases will have involvement of axillary nodes (of these approximately ⅓ to ¼ will survive 5 years and be free of disease if treated by radical mastectomy) and (b) maximum preoperative radiation will be effective in sterilizing the axilla in only 35 per cent of cases.

This is an experiment in therapy well worth careful inspection, but one which would scarcely be practical elsewhere with the widespread individual variations in surgical training and judgment that are present in most North American centers. McWhirter (13) quotes, quite possibly with correct emphasis, only strict survivals, but we have been conscious of the adverse psychologic effect in patients who might harbor residual disease and subsequently develop obvious local recurrence which would adversely affect their mental as well as their physical well-being. Consequently, because of the high incidence of local recurrence in our own cases (Table I) given a comparable dosage of high voltage radiotherapy and treated by simple mastectomy (23 per cent), as compared to patients in the same stages treated by radical mastectomy (6 per cent), we have attempted by adopting a more radical approach to the problem to increase the number of patients who are clinically free of disease during this period. There is, of course, no way of determining when residual disease in the axilla, walled off by the fibrous tissue reaction of the host to the tumor cells and to the high voltage therapy, will become an actively proliferating neoplasm again.

5. Depressed by the fact that 5 year survivals could not be obtained by radical mastectomy alone in certain groups of advanced or complicated breast cancer, Haagenson (7) and Grantley Taylor, among others, have chosen to exclude these cases from surgical treatment as a categorically inoperable group, thus attempting to improve their results by limiting drastically the indications for surgical treatment. By this method, 5 year survivals at these centers have increased from approximately 33 per cent to better than 50 per cent (Table IX).

TABLE I.—LOCAL RECURRENCE RATE IN MAMMARY CARCINOMA (83 CASES) TREATED WITH PREOPERATIVE RADIATION FROM 1933 TO 1943

Type of operation	No. of cases	No. of recurrences	Per cent of recurrences
Local excision	9	4	44
Simple mastectomy	26	6	23
Radical mastectomy	48	3	6

While appreciating the careful investigation and attention to detail that have made this striking improvement possible, we have attempted in direct contrast to broaden our scope of surgical treatment rather than limiting it, in order to bring as many patients as possible within the range of effective treatment. Once again, the test of time alone will point the correct approach to this problem.

6. In our own center, both surgeons and radiotherapists have for many years been impressed by the value of high voltage radiotherapy in destroying or devitalizing the cancer cell, and the problem of attempting to improve the results of treatment in breast cancer has been continuously approached as a joint responsibility of the Departments of Surgery and Radiotherapy. It is still our contention that the best results may be obtained by combining the use of radiotherapy and the radical surgical procedure, but it is of fundamental importance to stress the philosophy behind this radical approach, entailing as it does the use of a cancerocidal dose of x-ray therapy combined with a radical surgical procedure. Not even the most enthusiastic radiotherapists would suggest that high voltage radiotherapy alone could destroy or control a breast carcinoma indefinitely, and despite the routine use of a cancerocidal dosage of 4,200 to 4,500 roentgens delivered within 2½ weeks to the breast tumor, the skin of the breast, the chest wall and the axillary, supraclavicular and internal mammary nodes, viable carcinoma cells were found subsequently at the time of surgical treatment in 75 per cent of the breast tumors and 65 per cent of the axillas dissected. Presumably because of the accessibility to high voltage therapy, 50 per cent of the palpably involved supraclavicular nodes were clinically controlled 5 years or longer without recurrence.

Gordon Richards (18) reported originally in a Skinner lecture of 1947 the results of a combination of radical mastectomy and postoperative radiation, and these figures are reprinted in tabular form again (Table II), demonstrating an improvement from the general 5 year survival obtained by the radical operation alone of 33 per cent to a survival of 43 per cent in the entire group of 921 cases reported.

Although this result is a striking improvement, there were certain theoretic advantages to the use of radiation preoperatively (*vide infra*) which led to a thorough trial of the combination of preoperative high voltage radiotherapy followed by radical mastectomy.

THEORETICAL ADVANTAGES OF PREOPERATIVE RADIATION

I. Ability of radiation therapy to destroy the cancer cell (particularly the more rapidly growing cells).

II. Effectiveness of postradiation fibrosis in devitalizing the cancer cell: prevents local invasion by wall of fibrous tissue; prevents distant lymphatic embolism by constriction of lymphatics with perilymphatic fibrosis; possibly effects the cell by diminishing its blood supply.

III. Higher tumor dosage possible because radiation can be applied more effectively: with prominent breasts increasing effectiveness of tangential radiation, in areas not previously traumatized by surgical treatment, and to cells where blood supply has not been altered by operation.

IV. Normal tissue less receptive to implantation after preoperative radiation.

V. Devitalized cells spread by operative trauma innocuous.

VI. Regression of inoperable lesion may make surgical treatment possible.

VII. No delay in initiating treatment.

VIII. In patients who refuse any surgical treatment.

We, too, had been aware of the danger of spreading carcinoma by the operative insult to the axilla, and the possibility of tumor implants in the operative field at the time of operation. These factors might best be controlled it was believed by attempting to block the axillary lymphatic channels as a result of the reactionary contracting perilymphatic scarring prior to operation, and also by rendering any cells implanted locally or spread to a distance innocuous as the result of the radiation effect on the cell itself. In addition, it was known that both preoperative and postoperative radiation were capable of destroying or controlling the disease in the supraclavicular triangle in an appreciable number of cases as noted previously, and consequently, because the internal mammary chain lay in an anatomically constant position, no more than 1 inch from the midline and 1 inch in depth from the surface, high voltage radiotherapy could be applied to this region of potential involvement with considerable accuracy and with a reasonable expectation of similar control.

At the time of the original development of this technique, the Portmann classification was being used and preoperative treatment restricted to the stage III or advanced cases. When the results in this initial group of cases were assessed, it was discovered that the local recurrence rate of 5 per cent was less than the 10 per cent rate in stage II cases that had been treated by radical mastectomy followed by radiotherapy. In an attempt to discover what type of cases in stage II developed recurrences, a further division of that stage was made, dependent on the presence or absence of retraction phenomena related to the primary tumor. In those cases with no evidence of host reaction as demonstrated by the presence of contracting fibrous tissue proliferation, the local recurrence rate was only 2 per cent, whereas if retraction phenomena of this type were already detectable, there were local recurrences in 12.7 per cent of the cases. Consequently a new classification of the disease was evolved, based for the sake of simplicity on the presence or absence of retraction phenomena (taken to indicate an active reaction of the host to the presence of the malignant cell, with a definite fibrous tissue proliferation around

TABLE II.—RADICAL MASTECTOMY WITH POSTOPERATIVE RADIATION

Stage	Per cent 5 year survival	Per cent 10 year survival
I	81	59
II	54	28
III	38	21
IV	16	8
V	30	0
Total	43	26

TABLE III.—COMPARISON OF METHOD OF STAGING CARCINOMA OF BREAST

(Using Retraction and Invasion Phenomena as Determining Factors)

Stage	Steinthal	Stage	Portmann	Stage	Richards
I	Movable tumor alone	I	Movable tumor alone	I	Movable tumor alone
II	Tumor with or without retraction phenomena plus axillary nodes	II	Tumor with or without retraction phenomena plus axillary nodes	II	Movable tumor plus axillary nodes
III	Tumor with invasion phenomena with or without axillary nodes—plus distant metastases	III	Tumor with invasion phenomena with or without axillary nodes	III	Tumor with retraction phenomena with or without axillary nodes
		IV	As above—plus distant metastases	IV	Tumor with invasion phenomena with or without axillary nodes
				V	As above—plus distant metastases

the spreading neoplasm) or signs indicating actual invasion of tumor cells into the surrounding tissues or the local lymphatic plexuses (*vide infra*).

DESCRIPTIVE FEATURES OF THE LOCAL BREAST LESION

I. Retraction phenomena evidenced by: (1) Skin changes consisting of dimpling of skin demonstrated by approximation of fingers, elevation of arm above head, elevation of breast, contraction of pectoralis major; and nipple changes demonstrated by retraction and deviation. (2) Attachment to deeper structures demonstrated by limitation of mobility on contraction of pectoralis major, and actual movement of tumor on contraction of pectoralis major.

II. Neoplastic invasion evidenced by: (1) Skin changes consisting of ulceration, peau d'orange, brawny edema, inflammatory carcinoma, satellite nodules, Paget's disease. (2) Fixation to deeper structures shown when tumor becomes immobile.

In Tables III and IV this classification is presented and compared to the established Steinthal and Portmann classifications in general use elsewhere. Although the inadequacy of staging as a method of describing the individual lesion with reference to its biologic nature is recognized, this simplified classification is used in the statistical analysis that follows. In the present state of our knowledge it offers the only ordered method of reporting these results for an intelligent appraisal. From the progressive fall in 5 and 10 year survival rates (Table II), noted when the cases treated with postoperative radiation were staged in this manner, it was decided that it was a valid representation of an increasing extent of the disease process.

The possibility that the use of a cancerocidal dose of high voltage radiotherapy in the amount previously noted would have an adverse effect on subsequent surgical procedures has undoubtedly been a major factor in discouraging a more widespread adoption of this method of treatment. However, the various technical disadvantages enumerated below have not in this series represented serious hazards, nor have they interfered greatly with the wound healing.

TECHNICAL DISADVANTAGES OF PREOPERATIVE RADIATION

I. Increased technical difficulty at time of operation due to postradiation fibrosis.

II. Adverse effect on healing of wound—danger of tension and infection and necessity for more frequent use of skin graft.

III. Subsequent limitation of shoulder movement due to scarring in axilla.

IV. Increased incidence of edema of arm.

V. Possible psychologic result in delaying operation approximately 10–12 weeks.

VI. Length of treatment necessary and associated radiation sickness.

VII. Nursing difficulties in treating extensive superficial burn.

The operative dissection may be slightly more difficult, due to the reactionary fibrosis; but provided sharp dissection has been used throughout, no major problems have arisen and there has been no appreciable increase in the incidence of postoperative lymphedema or limitation of shoulder motion. In comparing two equal series of public ward patients, one treated by radical mastectomy and postoperative radiation (representing earlier and more localized stages of the disease) and the other with preoperative radiation followed by the radical operation, there were no significant statistical differences in the percentage of

primary healing or the period of hospitalization postoperatively.

ANALYSIS OF THE RESULTS OF TREATMENT OF BREAST CANCER WITH PREOPERATIVE RADIATION FOLLOWED BY RADICAL MASTECTOMY

The results obtained with this form of treatment have been summarized in tabular form in Tables V, VI, and VII. The method has of course been utilized largely for the more advanced cases, and of the entire 116 cases 80 fall into the stage IV grouping. Despite this high proportion of advanced cases, many of whom would fall into the categorically inoperable portion in Haagenson's classification (7), the 5 year survival rate remains at 40 per cent, and is almost identical with the 43 per cent survival in the group treated by postoperative radiation, where 80 per cent of the patients fell into the earlier stages of I to III in the Richards' classification (18). There remains, too, an appreciable 10 year salvage of 16 per cent in the entire group, and perhaps surprisingly enough 15 per cent of the stage IV patients also survived the 10 year period.

Although this method of handling the problem is designed to extend the scope of treatment and is primarily applicable to the advanced cases of stage IV, it will be noted that a few of the earlier cases were also treated by preoperative radiation. This was thought reasonable when the increased incidence of local recurrence was discovered in stage III cases treated postoperatively by high voltage radiotherapy as noted previously, and with this in mind any patient who demonstrates retraction phenomena as an indication of his reaction to an infiltrating neoplasm may well be benefited by preoperative radiation in an attempt to seal off lymphatic channels and render any locally disseminated cells innocuous. In a very few cases the lesion had been removed by excisional biopsy elsewhere several weeks previously, and because of the possibility of extensive permeation of the divided lymphatic channels it was decided preferable to give the patient preoperative radiation, even though the primary lesion may have fallen into stages I or II. The series also includes a small number of stage V cases, largely representing those patients in whom supraclavicular metastases

TABLE IV.—CLASSIFICATION OF STAGE OF DISEASE

Stage	Skin	Tumor	Metastases
I	Uninvolved	Localized, less than 3 cms.	None
II	Uninvolved	Localized, less than 6 cms.	Movable axillary nodes only
III (Signs indicate host reaction)	Retraction phenomena only	Attachment to fascia, greater than 6 cm.	With or without axillary nodes (if present may show evidence of retraction phenomena)
IV (Signs indicate spread of cancer)	Evidences of neoplastic invasion	Fixation to chest wall	With or without axillary nodes (if present may show signs of local neoplastic invasion)
V (Distant metastases)	As in any other stage	As in any other stage	Distant lymphatic metastases; supraclavicular nodes, contralateral axillary nodes, inguinal nodes, satellitic skin nodules beyond limits of breast Hematogenous metastases

appeared to be adequately controlled at the moment, or in whom a localized bony deposit had recalcified under treatment. Needless to say, the survival rate in this group is small (18 per cent) at 5 years, and no survivals are reported at 10 years. Consequently treatment in this type of case is to be considered only as a palliative form of therapy and is not in any way designed to prolong life. By far the largest proportion of these patients were those in whom a mastectomy was performed to remove an infected ulcerating lesion, which was making the patient ill because of the extensive mass of malignant cells and the presence of secondary infection. Ordinarily the mastectomy performed was the simplest possible, although occasionally a modified dissection of the axilla was also carried out, without removing the pectoralis major muscle, if there was a large mass in the axilla that was readily accessible.

The results are analyzed more specifically in Table VI, where an attempt is made to illustrate the percentage that are alive without evidence of residual or recurrent disease at the 5 and 10 year periods after treatment. It is, of course, in stage IV disease that these figures are most significant, and it is our belief that this form of therapy offers an opportunity not

TABLE V.—COMPARISON OF RESULTS OBTAINED WITH PREOPERATIVE AND POSTOPERATIVE RADIATION

Stage	5 year survival				10 year survival			
	Preoperative		Postoperative		Preoperative		Postoperative	
	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.
I-III	64	14	I 81	147	43	7	I 59	56
			II 54	193			II 28	92
			III 38	398			III 21	149
IV	41 26*	80	16	147	15 13*	40	8	45
V	18	22	30	36	0	10	0	12
Totals	40	116	43	921	16	57	26	354
IV & V	88		20		88		16	

*Cure rate, patient alive without evidence of recurrent or residual disease.

only of obtaining a survival for the period of years noted but also, and more importantly, offers the patient an opportunity of being free of disease even when the original lesion was of this advanced type. With 26 per cent free of disease at 5 years and 13 per cent at 10 years, it would appear that preoperative radiation and radical surgical measures offer the best warranty of freedom of disease yet reported in patients with advanced stages of breast cancer.

With increasing experience, both radiotherapeutic and surgical, in this combined form of attack on the problem, the techniques have become better standardized, and as might be expected with this technical improvement, as well as increasing confidence in the value of the method, there has been a definite improvement in the results obtained. In Table VII two consecutive equal series are compared with an improvement in the 5 year survival rate from 32.5 per cent in the earlier series to 50 per cent in the later one, with a similar though less marked improvement in the number of patients without residual or recurrent disease at this period. With this improvement in the 5 year results, it is probable, in view of the slight difference between survival and "cure" rate in the 10 year figures for the original series, that the 10 year results for the second series and for the whole group will show a similar improvement.

Not only has the combination of surgery and high voltage radiotherapy improved our survival statistics, but we think it is of some importance that the incidence of local recurrence is also markedly improved (Table

TABLE VI.—COMPARISON OF RESULTS OBTAINED WITH PREOPERATIVE AND POSTOPERATIVE RADIATION

Stage	5 year survival				10 year survival			
	Preoperative		Postoperative		Preoperative		Postoperative	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
I-III	14 patients 9 survivals	64	I 147	81	7 patients 3 survivals	43	I 56	59
			II 193	54			II 92	28
	2 D.E.D.* Net survival 9 of 12	75	III 398	38	1 D.E.D.* 1 Untraced Net survival 3 of 5	60	III 149	21
IV	80 patients 33 survivals	41	147	16	40 patients 6 survivals	15	45	8
	3 D.E.D.* Net survival 33 of 77 20 A. & W.	43 26†			3 D.E.D.* Net survival 6 of 37 5 A. & W.	16 13†		
V	22 patients 4 survivals	18	36	3	10 patients 0 survivals		12	0
	2 D.E.D.* Net survival 4 of 20	20						
Totals	116 patients 46 survivals	40	921	43	57 patients 9 survivals	16	354	26

*D.E.D., died of extraneous disease.
†Cure rate, patient alive without evidence of recurrent or residual disease.

VIII). Particularly is this true with the utilization of preoperative radiation where the local recurrence rate remains at a relatively low level of 12.3 per cent, despite the fact that better than 80 per cent of the patients so treated had advanced stages of the local lesion. In the earlier stages in which postoperative radiation has been delivered to the operative site, the recurrence rate similarly is only 10.5 per cent, both these figures being comparable to the figures quoted by Haagenson (7) and Grantley Taylor, who have excluded the categorically inoperable lesions from surgical treatment. Despite the delivery of a cancerocidal dose (at least as heavy as that which can be delivered postoperatively), we have been impressed by the relatively high incidence of local recurrences in the late stages of the disease, when the local lesion was treated by simple mastectomy. A value of 31.4 per cent makes it difficult to contemplate, other than with some caution, the use of simple mastectomy in lesions of less advanced degree.

Finally in Table IX, a comparison of the reported results of treatment in carcinoma of the breast by the methods commonly in use today is presented. Despite the very high percentage of cases (88 per cent) falling into stages IV or V of the Richards' classification (18), the 5 and 10 year survivals are in every way comparable with those reported by McWhirter (14) without the objections noted previously, and in addition approximate our own results previously reported concerning the use of postoperative radiation, in which series only 18 per cent of the patients fell into the last two stages of disease. The fact that many of these patients in the late stages would fall into the "categorically inoperable"

TABLE VII.—IMPROVEMENT IN RESULTS IN TWO CONSECUTIVE SERIES OF STAGE IV MAMMARY CARCINOMAS

Results	1933–1941 40 cases		1942–1946 40 cases		Total 80 cases	
	Per cent	No.	Per cent	No.	Per cent	No.
5 year survival rate	32.5	13	50	20	41	33
Cure rate* (gross)	22.5	9	27.5	11	25	20
10 year survival rate	15	6	Results not yet available			
Cure rate* (gross)	12.5	5				

*Cure rate, patient alive without evidence of recurrent or residual disease.

TABLE VIII.—COMPARISON OF LOCAL RECURRENCE RATES WITH DIFFERENT METHODS OF TREATMENT

Treatment	Surgeon	Per cent
Before era of radical mastectomy		62–82
Radical mastectomy Johns Hopkins Hospital	Halsted (wide skin incision)	31.9
(No selection)	Lewis & Rienhof (plastic skin closure)	39.7
Roosevelt Hospital	White	22.6
Presbyterian Hospital	Haagenson & Stout Early series	22.8
	With more careful selection and attention to operative detail	12.5
Massachusetts General Hospital	Taylor Selected cases	11
Combination of mastectomy and radiation therapy Radical mastectomy with postoperative radiation (23% stages IV & V)		10.5
Preoperative radiation with radical mastectomy (83% stages IV & V)		12.3
Preoperative radiation with simple mastectomy (stages IV & V only)		31.4

TABLE IX.—COMPARISON OF RESULTS OF DIFFERENT METHODS OF TREATMENT

Method	5 year survival Per cent	10 year surviva Per cent	Type of cases Per cent
Untreated Daland	22	1	
Nathanson & Welch	19	5 (graph)	All cases
Surgery alone Collected data	33	32 (With involvement of axillary nodes Presbyterian Hospital 20%; Memorial Hospital, 21%)	Cases selected for radical mastectomy (mostly stages I-III)
Presbyterian Hospital (excluding categorically inoperable group	50		
Radical mastectomy Postoperative radiation (Toronto General Hospital)	43	26 (With involvement of axillary nodes, 23%)	82 (Stages I–III) 18 (Stages IV–V)
Radical mastectomy Preoperative radiation	40	16	88 (Stages IV & V)
Simple mastectomy Postoperative radiation (McWhirter)	42	25	All cases (56% "operable" group)

group of Haagenson (7) detracts from the impressive improvement in the results obtained when the cases treated surgically are so carefully selected, and we believe the results offer some encouragement in extending the scope of treatment rather than attempting to limit it. The combination of radical high voltage radiotherapy and subsequent radical surgical treatment would appear to be the determining factor that makes this extension possible.

Consequently we now advise almost routine use of preoperative radiation in stage IV lesions (see summary), with the possible exception of very elderly patients who harbor such a lesion of long standing and obviously of low biologic activity, particularly if associated with a marked fibrous tissue reaction indicating a favorable reaction to the local malignancy on the part of the host. In view of the appreciable incidence of local recurrence in stage III cases treated with postoperative radiation (12.7 per cent), we have tentatively extended the indication for preoperative high voltage radiotherapy to include those cases exhibiting retraction phenomena, which would seem to indicate infiltrating carcinoma at points of potential danger if surgical treatment were carried out without initial protection by reactionary perilymphatic fibrosis. Thus one would advise preoperative radiotherapy in cases showing retraction phenomena around involved lymphatic nodes in the axilla, and also with lesions of similar type in the medial quadrants adjacent to possible paths of internal mammary node involvement, particularly when changes were apparent in the axillary nodal area indicating extensive lymphatic permeation or embolism. If the results continue to warrant adoption of this plan of therapy, it is quite possible that preoperative radiation will be advised for any stage III lesion in which the axillary nodes are clinically involved. The occasional very large primary tumor, in which no other clinical stigmas of malignancy such as retraction or invasion phenomena are apparent (usually because of the depth of the lesion within the breast tissue), is included in stage III and treated preoperatively because of the pathologic proof that lesions larger than 6 centimeters commonly show extensive lymphatic involvement, even though clinical evidence of this involvement is not apparent.

PRESENT PLAN OF TREATMENT IN DIFFERENT STAGES

Stage I. Radical mastectomy, no radiation therapy. Diagnosis verified by incisional biopsy at time of mastectomy.

Stage II. Radical mastectomy with postoperative radiation. Use of radiation therapy depends upon pathologic proof of axillary node involvement.

Stage III. Treatment varies: (a) Preoperative radiation followed by radical mastectomy when: (1) tumor larger than 6 centimeters in diameter (clinical measurement) with or without retraction phenomena or axillary nodal involvement; (2) tumor smaller than 6 centimeters in diameter associated with axillary nodal involvement which shows definite retraction phenomena; (3) small tumor in medial quadrants of breast showing retraction phenomena and also definite axillary nodal involvement. (b) Radical mastectomy with postoperative radiation when: (1) tumor smaller than 6 centimeters with retraction phenomena, with or without movable axillary nodes, in outer quadrant of breast; (2) small tumor with retraction phenomena but no clinical nodal involvement.

Stage IV. Preoperative radiation followed by radical mastectomy. Diagnosis verified by aspiration biopsy 10 days to 2 weeks after beginning treatment.

Stage V. Primarily radiation therapy to local breast lesion, skin of chest wall, axillary, supraclavicular, and internal mammary nodal areas. Surgical or hormonal therapy may be indicated in the following conditions: (a) Surgical treatment: (1) if involved supraclavicular nodes controlled by radiation therapy may subsequently advise mastectomy if it is thought patient will be benefited by removal of extensive lesion in breast or axilla (occasionally utilize simple mastectomy with modified axillary dissection); (2) in fungating or ulcerating lesion with secondary infection, advise preoperative radiation followed if necessary by simple mastectomy or if difficult to deliver effective radiation may do simple mastectomy alone. (b) Hormonal therapy supplementing extra ports of radiation therapy: (1) distant lymphatic metastases with contralateral axillary or inguinal nodal involvement or satellite skin nodules beyond limits of usual ports; (2) hematogenous metastases—lung, hormonal therapy—bones, radiation therapy (200 K.V.) with hormonal therapy if bone involvement widespread.

SUMMARY

1. The importance of carcinoma of the breast is stressed as one of the prime killing diseases in women between the ages of 30 and 75 years.

2. Reasons for the recent dissatisfaction with surgical treatment alone as the method of treatment for all cases of breast cancer are briefly reviewed.

3. The possible causes of death resulting from the disease despite surgical treatment are presented and discussed.

4. The various methods of attempting to control these causes of death are enumerated, and the rationale of the different approaches to the problem mentioned.

5. The theoretic advantages of preoperative radiation are outlined and it is stressed that the technical disadvantages as they affect subsequent surgical treatment have been overemphasized in previous literature.

6. The results of treatment of breast cancer, utilizing a combination of preoperative radiotherapy and radical mastectomy, are presented and outlined in a staging designed for this purpose and previously reported by Richards.

7. These results are compared with those obtained by other methods of treatment.

8. A final plan is presented, outlining the method of treatment advised in the various stages of disease in this one center.

9. It is believed that these results indicate that further consideration of the value of preoperative radiation is warranted.

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ARTERIAL EMBOLISM WITH NOTES ON OPERATIVE AND ANTICOAGULANT THERAPY

WILLIAM C. McGARITY, M.D., and ROY L. ROBERTSON, M.D., F.A.C.S.,
Atlanta, Georgia

ARTERIAL embolism has in the past exacted a high toll of lives and limbs. Within the past decade the use of newer techniques of treatment in the field of cardiovascular surgery has reduced morbidity and mortality. The purpose of this report is to present a case treated in accordance with the more recent trends of surgical management.

For detailed discussions of the problems of etiology, pathology, diagnosis, and management of arterial embolism, the reader may refer to the excellent reviews by Warren and Linton, Haimovici, Veal and Dugan, and Massell. This paper primarily presents a case of multiple arterial embolism with discussion of the above problems only insofar as they relate to the case report.

Multiple arterial embolism, while unusual, is by no means rare, as evidenced by previous case reports of Deitch, Groth, MacFarlane, Scott and Williams, Eddy and Congdon, Fidian, and Proffitt and associates. This additional case is of interest for several reasons: (1) the occurrence at close intervals of 3 operable emboli in the lower extremities; (2) the significance of heparin therapy in the prevention of propagating thrombi adjacent to the embolus; (3) the utilization in 1 case of different surgical techniques; (4) the salvage of both lower extremities as a result of prompt surgical management.

CASE REPORT

W. D. S., a 42 year old married textile worker, was referred by her local physician to Emory University Hospital, December 3, 1951. Eight hours prior to admission, while at work, she had noted sudden pain in the anterior right thigh followed shortly by numbness, weakness, and coolness of the right lower leg. Within an hour the foot and leg changed in appearance from pallor to mottled cyanosis.

From the Whitehead Department of Surgery, Emory University School of Medicine, Emory University, Georgia.

Her past history was indicative of myocardial infarction approximately 3 weeks previously.

On admission her temperature was 98.6 degrees; pulse 124 and regular; blood pressure 160 systolic, 110 diastolic in both arms. The heart was enlarged with evidence of aortic stenosis and mitral regurgitation. The right leg was moderately cyanotic and cool from the knee distally with tenderness in the calf. A right femoral pulse was palpable immediately below the inguinal ligament, but no pulses were felt beyond this point. The left leg was of normal color and temperature with all pulses present.

An electrocardiogram substantiated evidence of recent subendocardial myocardial infarction. Oscillometric studies revealed absence of pulsations at the right knee and ankle with normal findings on the left leg. Skin surface temperatures in the right leg were approximately 10 degrees lower than comparable points on the left (Fig. 1a).

A diagnosis of peripheral arterial embolism of the right common femoral artery was made. It was thought that the embolus had originated from a mural thrombus in the heart.

Twelve hours after onset of symptoms an embolectomy was performed under local anesthesia. The vessels were exposed by a vertical incision in the upper thigh and the superficial femoral, profunda, and common femoral arteries were isolated and controlled with soft rubber tourniquets. An arteriotomy was performed just above the bifurcation, and a short proximal fresh thrombus together with a Y-shaped embolus were removed (Fig. 2). There was brisk bleeding from the proximal artery. Since there was no retrograde flow from the superficial femoral artery, a fresh thrombus was believed to be present distally. After an unsuccessful attempt was made to remove this by suction with a small rubber catheter, the posterior tibial artery was exposed at the ankle, a large metal cannula was inserted, pointed proximally, and the distal arterial tree was forcefully irrigated with a solution of 50 milligrams of heparin in 500 cubic centimeters of 0.9 per cent saline. This maneuver, together with gentle milking of the superficial femoral artery, dislodged a distal thrombus 28 centimeters in length (Fig. 2). Following its removal, there was good retrograde bleeding from the superficial femoral artery. All vessels were irrigated with the heparin and saline solution as before, and the arteriotomy was closed with a continuous everting suture of No. 00000 arterial silk. Upon release of the tourniquets, good pulsations were noted in all vessels. Fifty milligrams of heparin were given

intravenously as the artery was closed. No undue bleeding from the vessel or wound was noted. A soft rubber drain was placed beneath the deep fascia and the wound was closed in layers with interrupted sutures of silk.

Postoperatively, heparin was administered as intermittent injections every 4 to 6 hours and the Lee-White coagulation time was kept within 40 to 80 minutes. Immediately following the operation, the right lower leg became warm and of normal color. The dorsalis pedis and popliteal pulses were palpable 8 hours after the operation.

Repeated observations, including determinations of skin surface temperatures and oscillometric readings during the next 5 days, showed the leg to be essentially normal (Fig. 1a). The drain and sutures were removed on the sixth day.

On the morning of the fifth postoperative day the patient developed sudden pain in the left leg, followed by numbness, coolness, and mild cyanosis. One hour later, examination revealed changes identical to those previously observed in the right leg. A diagnosis of arterial embolism involving the left common femoral artery was made. Six hours after the onset of symptoms she was in the operating room.

Re-examination of the left leg revealed that it had regained normal color and temperature and that a dorsalis pedis pulse was palpable. These findings were confirmed by instrumental study (Fig. 1b). The embolus was believed to have shifted or progressed distally involving either the lower femoral or popliteal arteries. As such, conservative therapy rather than surgery was indicated.

The patient was returned to her room under close observation. Her left leg remained warm, with good motion and palpable pulses at the ankle, until approximately 15 hours after the onset of the first symptoms. At this time she again noticed pain in the left leg with coolness and cyanosis. Examination revealed a picture identical to that earlier in the day; no pulses were palpable beyond the left inguinal ligament. Eighteen hours after the initial onset, a left femoral embolectomy was performed under local anesthesia. A large cup-shaped embolus measuring approximately 3 centimeters in length was removed from the left common femoral artery (Fig. 3). It extended for a short distance into both superficial and profunda femoral arteries. The embolus was *not* adherent to the wall of the artery and *no* distal or proximal thrombus was present. The proximal and distal vessels bled freely. Additional heparin was given intravenously and the arteriotomy was closed with a continuous everting suture of No. 00000 arterial silk.

Postoperative clinical and instrumental findings in the left lower extremity were normal (Fig. 1b). Heparin therapy was continued and oral dicumarol (3,3′ methylenebis [4-hydroxycoumarin]) was begun. After 3 days an adequate dicumarol effect was obtained and heparin was discontinued. Prothrombin concentration was maintained between 10 and 20 per cent of normal.

On the sixth postoperative day when the drain and sutures were removed both incisions had healed well. The patient's hospital course was uneventful and she was discharged on December 22, 1951, 12 days following her second operation, with a total hospital stay of 19 days. At the time of discharge both lower extremities were essentially normal. All peripheral pulses were present except in the right posterior tibial artery, which had been sacrificed in the first operation.

She was seen twice during the following month and had no complaints referable to the lower extremities. All pulses were palpable and she was able to walk and stand for considerable periods of time without difficulty. Repeated oscillometric studies revealed good pulsations at the knee and ankle in both legs.

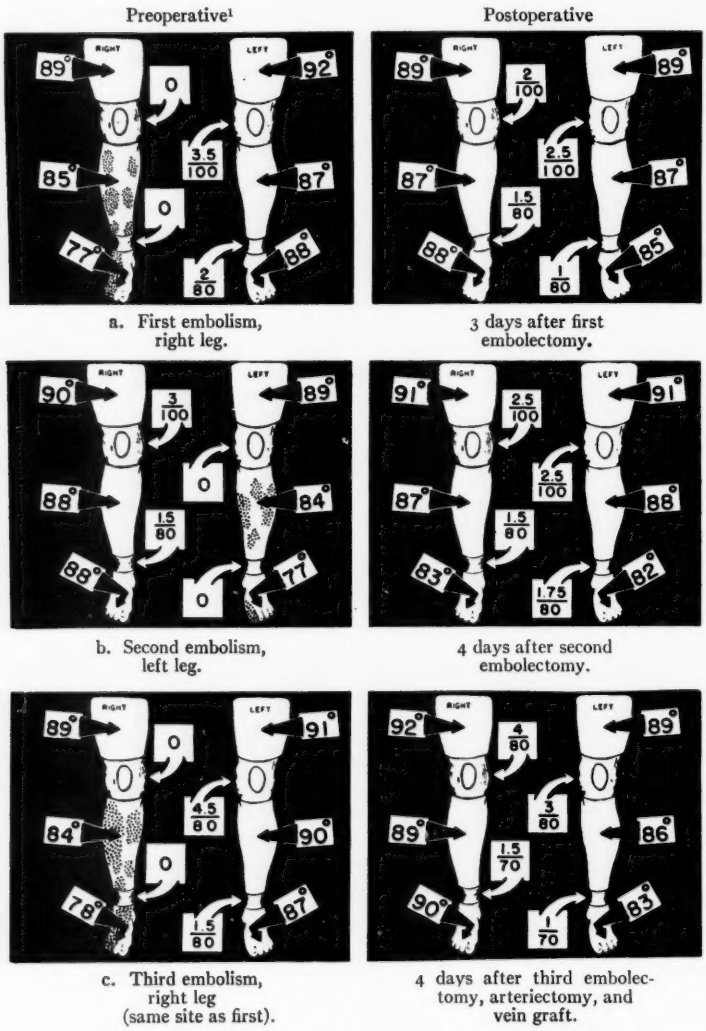
On February 9, 1952, the patient was readmitted because of congestive heart failure. She had marked pitting edema of both lower legs. All peripheral pulses were present, however, and there appeared to be no impairment of the arterial circulation. Digitalization and mercurial diuretics produced marked improvement and the edema disappeared.

On the third hospital day sudden numbness and coolness of the right leg and foot developed. At first there was no pain; however, after 2 hours the patient complained of discomfort in the right calf and foot. An hour later mottled cyanosis appeared.

Upon examination a pulse was felt just below the right inguinal ligament; beyond this point no pulses were palpable. Skin surface temperatures were markedly decreased and oscillometric studies revealed no pulsations at the right knee or ankle (Fig. 1c). The left leg was essentially normal. The diagnosis was made of embolism in the right common femoral artery, at the identical site of the first episode.

Five hours after the onset of symptoms the patient was taken to the operating room. Under local anesthesia the arteries in the right groin were exposed and controlled by the application of soft rubber tourniquets. There was a mass palpable in the common femoral artery just proximal to the old arteriotomy incision. An arteriotomy was performed immediately above the site of the old incision and it was noted, as the fibrous tissue about the vessel was dissected away, that the wall was quite thin. An embolus approximately 3 centimeters in length with short propagating distal and proximal thrombi was removed. There was adequate proximal and retrograde flow of blood. Because of the thinness and friability of the arterial wall it was impossible to close the artery adequately.

An arteriectomy was performed. The entire common femoral artery was resected including a short portion of the external iliac artery, the bifurcation of the common femoral artery, a portion of the profunda, and superficial femoral arteries. It was thought that even if all available collaterals were preserved by the use of anticoagulants, circulation to the limb would still be inadequate if the artery



a. First embolism, right leg.

3 days after first embolectomy.

b. Second embolism, left leg.

4 days after second embolectomy.

c. Third embolism, right leg (same site as first).

4 days after third embolectomy, arteriectomy, and vein graft.

Fig. 1. Serial studies of skin surface temperatures and oscillometry.

[1]Note absence of pulsations at knee and ankle, lowered skin temperatures, and mottled cyanosis in affected extremities during all embolic episodes.

was ligated. Therefore, the continuity of the artery was re-established by means of a vein graft. A segment of superficial femoral vein, approximately 8 centimeters in length, was obtained from the area just distal to the profunda vein down to a bifurcation of the vein (Fig. 4). The vein segment was reversed to prevent obstruction by the valves. End-to-end anastomosis was performed, everting mattress sutures of No. ooooo silk being used.

The patient was given heparin intravenously and the vein graft was filled with a heparin and saline solution. Upon removal of the clamps, good pulsations were evident in both the graft and distal arteries. The wound was closed in layers with sutures of silk.

Following the operation the foot and leg regained normal temperature and color, and both a dorsalis pedis and popliteal pulse were palpable. The pa-

tient was maintained on intermittent injections of aqueous heparin and oral dicumarol therapy was begun on the first postoperative day. Heparin was discontinued on the third day when a prothrombin concentration of 10 to 20 per cent of normal was obtained. Convalescence was uneventful. The color of the right leg remained normal and skin temperatures were slightly higher than on the left leg (Fig. 1c). Sutures were removed on the sixth postoperative day. There was no evidence of bleeding or infection. The patient was allowed to be up on the tenth hospital day and was able to walk without difficulty, the only complaint being mild weakness of the right leg (Fig. 5).

Daily doses of dicumarol were continued for 6 months and plasma prothrombin concentration was maintained between 10 and 20 per cent of normal. Eight months following her last operation, the patient was asymptomatic and carrying out household duties. Repeated examinations have revealed normal arterial circulation in both legs.

DISCUSSION

Sixty to 90 per cent of the peripheral arterial emboli are reported to originate in the heart as clots in the auricles in the presence of irregular heart action, or as mural thrombi following myocardial infarction. Less frequent causes are vegetations in endocarditis and thrombi formed on sclerotic plaques in the great vessels.

Approximately two thirds of arterial emboli migrate to the extremities; the remainder involve visceral or cerebral vessels. Multiple embolism is not rare: a series of 228 patients reported by Haimovici had a total of 443 emboli, peripheral and visceral.

Arterial thrombosis or acute thrombophlebitis with vasospasm may at times closely simulate arterial embolism. The differential diagnosis between arterial embolism, arterial thrombosis, and acute thrombophlebitis can usually be determined by a detailed history, complete physical examination, and instrumental studies (skin temperatures and oscillometry). In arterial embolism pain in the extremity is the first symptom in the majority of cases. Pain is followed by coolness, cyanosis, numbness, and weakness. In the case presented, sudden pain was an initial symptom in the first 2 embolic accidents but was delayed several hours in the third. Presence or absence of pulsations distal to the obstruction were verified by oscillometric studies (Fig. 6).

Fig. 2. Embolus with short proximal and long distal propagating thrombi removed from right femoral artery at first operation. Note the Y-shape of the embolus conforming to bifurcation of common femoral artery. The distal thrombus measured 28 centimeters in length.

The local changes which occur follow a set pattern. First, the embolus creates a mechanical obstruction. Emboli tend to lodge at a bifurcation and the circulation is cut off in both main branches of the affected artery. Second, marked arterial spasm, reflex in origin and initiated by local stimuli to the sensory fibers in the arterial wall, develops distal to the embolus. The arterial spasm may persist for hours or even days following embolectomy. Third, fresh thrombi may form quickly and propagate both proximally and distally. The presence of mechanical obstruction, slowing of distal blood flow, marked arterial spasm, and apparent increased coagulability of the blood all act together to promote this secondary thrombosis. The proximal thrombus as a rule is short and extends up to the first large branch above the embolus. Distal thrombi may propagate 25 centimeters or more, through the distal arterial tree, cutting off the collateral channels one by one. The progression of these factors, if unchecked, leads to the development of gangrene.

The treatment of arterial embolism may be divided into three groups. In two of these conservative therapy alone is indicated. First, there are patients so critically ill from other disease or from simultaneous cerebral or visceral embolism that any but supportive treatment may be hazardous. In the second group are those in whom circulation in the extremity is adequate. In the conservative treatment of this group, the use of anticoagulants is imperative to prevent propagation of thrombi and to insure the patency of collaterals. Other adjuncts include the oscillating bed and sympathetic interruption. However, once anticoagulant therapy is begun, sympathetic blocks are contraindicated. Systemic vaso-

Fig. 3. Embolus removed at second operation from left femoral artery. Note absence of thrombi, also cup-shaped outline which apparently allowed some blood to flow past during the interval of remission of signs.

dilator drugs are not recommended as a rule because generalized vasodilatation tends to decrease blood flow to the affected extremity.

In the third, or surgically treated group, five procedures may be used: (1) Embolectomy, as the preferable procedure, should be performed when possible. (2) Arteriectomy may be necessary if local conditions make closure of the arteriotomy impossible. Arteriectomy may remove the local stimulus for vasospasm and decrease incidence of propagating clots; in addition, periarterial sympathectomy is accomplished and may lead to increased distal blood flow. (3) Following arteriectomy, continuity may be restored by end-to-end anastomosis or by bridging the defect with an artery or vein graft. (4) Permanent interruption of sympathetic pathways, rather than embolectomy, may be indicated when smaller arteries, such as the popliteal, are involved. Procaine injections, as a primary therapeutic trial, usually precede this procedure. (5) Amputation becomes necessary if gangrene is present.

A comparison of the results of various forms of treatment has been made by Warren and Linton. Their surgical cases had a limb salvage of 86 per cent as compared with 66 per cent treated by conservative methods. In this latter group there is no mention of residual or arterial insufficiency. A similar series reported by Reynolds and Jirka is in close agreement. The late results following embolectomy, according to Strombeck, indicate an average life expectancy of only a few years, with the majority of deaths due to heart disease or cerebral embolism.

The case which has been presented is typical as regards etiology, history, presenting symptoms, and diagnosis. The distribution of emboli bears out the observations of others that one-half to two-thirds involve the major vessels of the lower extremities. The occurrence of 2 embolizations in the same artery, even in the same area, is not in itself unusual; however, the presence of sclerotic change in the wall of the artery at the time of the second procedure on the right femoral artery presented a technical problem. This was thought to be due to the earlier removal of adventitia with resultant alteration in nutrition of the tissues in the outer coats of the vessel.

After removal of fibrous tissue about the vessel during the second operation on the right femoral artery, the vessel wall was quite thin and consisted chiefly of media and intima. Because an attempt at closure was unsuccessful, one of two decisions became necessary: (1) to perform an arteriectomy, ligate the main artery close to its major branches, and depend upon anticoagulants and collateral circulation; or (2) to attempt restoration of arterial continuity. Since the patient was in

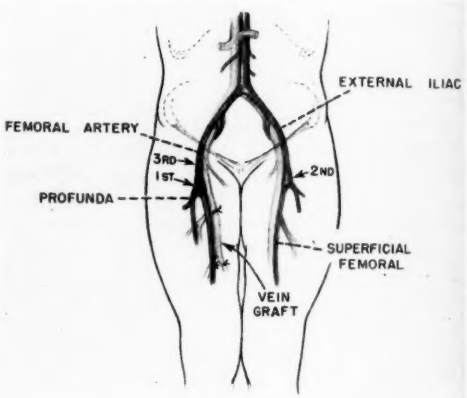


Fig. 4. Diagrammatic sketch depicting site of 3 emboli and origin of vein graft in third operation.

reasonably good condition and the procedure was being performed under local anesthesia and since collateral circulation was deemed inadequate to supply the needs of the limb, it was decided to attempt the use of a vein graft. With the availability of vessel banks, arteriectomy with re-establishment of continuity by grafting may be used more frequently in cases in which closure is impossible.

Anticoagulants were used throughout each hospitalization before, during, and after the various surgical procedures. At all the operations, a solution of 50 milligrams of heparin in 100 cubic centimeters of 0.9 per cent saline was used locally for irrigation of the affected vessels, and heparin was given intravenously as soon as the clots were removed and before the vessels were repaired. This is an important factor in preventing the formation of fresh thrombi at the site of closure. Following heparinization, no difficulty with hemostasis at the operative incisions has been encountered. With a soft rubber drain left in the wound, if hemorrhage should occur it can be detected early and before a large hematoma can form. Pulmonary emboli are not uncommon in the postoperative course of these patients and their prevention is likewise important. The use of anticoagulants is of prophylactic value in this regard.

Fig. 5. Photograph of patient after third operation showing types of incisions used.

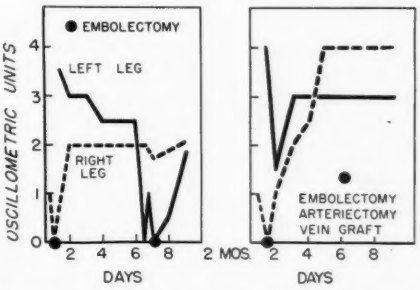


Fig. 6. Graphic representation of changes in oscillometric pulsations at each knee during two hospitalizations.

While heparin is necessary because of its rapid action and the immediate protection which it affords, it need not be continued past the time required for acquisition of therapeutic levels with a longer acting anticoagulant. Heparin is best given by intermittent intravenous or intramuscular methods, amounts which will cover the patient adequately for 4 to 6 hours being used. Such usage tends to minimize the high peak effects that are obtained when heparin in menstruum—which also carries a greater risk of bleeding—is used.

From the standpoint of local surgical procedures (embolectomy or arteriectomy), it may not be necessary to continue anticoagulants for longer than 3 weeks. However, for prophylaxis against further embolism, it may be desirable to continue dicumarol for several months.

It is interesting to compare the local conditions at the first and second embolectomies. At the first embolectomy, 12 hours following onset of symptoms, a distal thrombus measuring 28 centimeters in length and a shorter proximal thrombus were present. At the second embolectomy, 18 hours following onset of symptoms, and with the patient on therapeutic dosages of heparin, no fresh thrombus was present nor was the embolus adherent to the wall of the artery—a striking demonstration of the value of anticoagulant therapy.

SUMMARY

1. Peripheral arterial embolism must be considered a surgical emergency; if surgery is

indicated every attempt should be made to operate as soon as possible.

2. Heparin therapy should be begun immediately and continued with administration preceding the operation preferably by 1½ to 2 hours.

3. Heparin should be used during the operative procedure both locally and systemically to prevent recurrent thrombosis. Long term postoperative anticoagulant therapy should be planned and carefully followed.

4. Every effort should be made to preserve or restore continuity of the artery.

5. Local anesthesia is the agent of choice. This case demonstrates that its use is feasible even when a vessel such as the external iliac is involved.

6. In each case of arterial embolism, the possible occurrence of multiple emboli must be considered and appropriate therapy held in readiness.

Experience with this case might suggest that in the management of re-embolization involving an identical site in one artery, the problem could be more conveniently handled by making the second arteriotomy incision at a point above or below any possible changes in the vessel wall (in this instance, the external iliac or the superficial femoral). From available reports in the literature, this case constitutes one of the first in which re-establishment of arterial continuity by vein graft was necessary in the management of peripheral arterial embolism.

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THE EXPERIMENTAL PRODUCTION OF HIGH INTERVENTRICULAR SEPTAL DEFECTS

A Physiological and Pathological Study

JEROME HAROLD KAY, M.D., VIVIEN THOMAS, and
ALFRED BLALOCK, M.D., F.A.C.S., Baltimore, Maryland

THE present study was undertaken in order to develop a method for producing high ventricular septal defects of uniform size that would remain patent and in order to study the physiologic and pathologic changes that accompany such defects.

METHODS

After employing several methods with only moderate success, it was found that the best method consisted of using an instrument similar to a sharpened cork borer. An interventricular septal defect could be produced by inserting the instrument through the right ventricular wall and exerting pressure and suction on the instrument while making a rotary motion. After the instrument engaged the septum suction was applied to the opposite end of the cardiotome in order to engage and remove a large portion of the septum. The instruments which were of various sizes were made of steel and sharpened at the tip end. By trial it was determined that the largest sized instrument we could use without producing cardiac failure immediately or within a few days was a cardiotome, 3/8 inch (9.3 mm.) in diameter (Fig. 1).

Adult mongrel dogs varying in weight from 13 to 25 kilograms were used in the majority of the experiments. After induction with open drop ether, an endotracheal tube with an inflatable cuff was introduced, and positive pressure ether anesthesia was employed. The chest was opened through the left fourth interspace and the pericardium was incised anterior to the left phrenic nerve. A mattress suture of silk was placed in the right ventricular muscle immediately proximal to the origin of the pulmonary artery. A pursestring suture of silk was placed around the mattress suture. These sutures did not pierce the endocardium. The loose ends and the loop of the mattress suture were pulled taut and an incision, large enough to admit the tip of the left index finger, was made through the right ventricular muscle. The tip of the left index finger was inserted and as it was withdrawn, the cardiotome was inserted. The pursestring suture was then pulled taut to control bleeding. The instrument was advanced until it engaged the interventricular septum immediately beneath the pulmonary valves. At this time suction was started and, using a rotary motion, the instrument was advanced through the interventricular septum. An attempt was made to direct it so that it emerged immediately beneath the aortic valves in the left ventricular cavity. This maneuver produced defects high in the septum—the most frequent anatomical position of congenital interventricular septal defects (Figs. 2 and 3). The suction was continued as the instrument was withdrawn from the right ventricle and, at the same time, the left index finger was inserted and the defect was dilated. The finger was removed and the previously placed mattress and pursestring sutures were tied. The incisions in the pericardium and chest wall were closed.

The plug of septal tissue which was removed was usually firmly held in the instrument. It was conical in shape and was the size of the instrument on the right ventricular side and was approximately 1⅓ times the diameter of cardiotome on the left ventricular side. The plug was larger on the left ventricular side because of the suction which had been applied during the advancement of the instrument.

From the Department of Surgery of the Johns Hopkins University and Hospital. Aided by a grant from the United States Public Health Service, National Heart Institute, H-226 (C2).

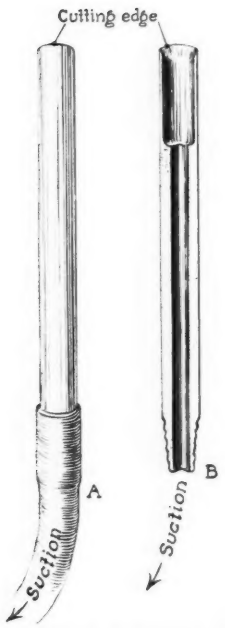


Fig. 1. Diagram of the instrument used to produce an interventricular septal defect. A, Outside of instrument with rubber tubing leading to suction apparatus. B, Sagittal section.

Examination of the hearts of the animals that died immediately following the procedure revealed that the defect produced was oval in shape, the width being slightly larger than the diameter of the instrument used.

Cardiac catheterization was performed 8 to 12 months postoperatively in 9 of the dogs. Sodium pentobarbital was used as the anesthetic agent except on 2 occasions when morphine and atropine were used to sedate the animals. Pressures in the right atrium, right ventricle, pulmonary artery, as well as the femoral artery were measured with a capacitance manometer and recorded with a direct writing oscillograph. Blood samples were obtained during cardiac catheterization and blood oxygen gas analyses were performed with the Van Slyke apparatus and the Beckman spectrophotometer (4). The cardiac output and quantity of blood shunted through the defects were determined by application of the Fick principle.

RESULTS

Operations were performed on 32 animals, and 19 survived for 48 days or more following the creation of the defect. The survival rate varied directly with the size of the defect created.

An instrument ½ inch (12½ mm.) in diameter was used to produce an interventricular septal defect in the first 4 dogs. These animals weighed between 15 and 25 kilograms. Because the defect created in these dogs was too large, 3 of the 4 died within the first 24 hours of right-sided heart failure. The fourth dog was sacrificed on the 76th postoperative day because of pronounced right-sided failure. Prior to death there was an excellent thrill and systolic murmur to the left of the sternum in the left fourth interspace. There was 4 plus pitting edema of the posterior extremities and ascites was pronounced. At autopsy there was hepatomegaly but no evidence of splenomegaly. The interventricular septal defect was located immediately beneath the pulmonic and aortic valves and readily admitted an instrument which was 7/16 inch in diameter. It was well endothelialized. During the creation of the defect the interventricular septal plug was not recovered and at autopsy it was found attached to the border of the defect; it had so completely atrophied that it was a white piece of scar tissue approximately one-fourth the size of the defect. It was so attached that it did not reduce the size of the defect significantly.

An instrument 7/16 inch (10.9 mm.) in diameter was used to produce an interventricular septal defect in 3 dogs ranging in size from 14 to 18 kilograms. All 3 dogs died of right-sided failure within 24 hours.

In the remaining 25 dogs a cardiotome 3/8 inch in diameter was used. Nine of the dogs died within 13 days. The most common causes of death were congestive failure, postoperative hemorrhage from the myocardial incision, and distemper.

Three dogs were sacrificed between the second and the fifth months because no thrill or murmur was present. At autopsy the defects were found to have healed completely. In all 3 of these the defect had been placed too far anteriorly so that it involved not only the

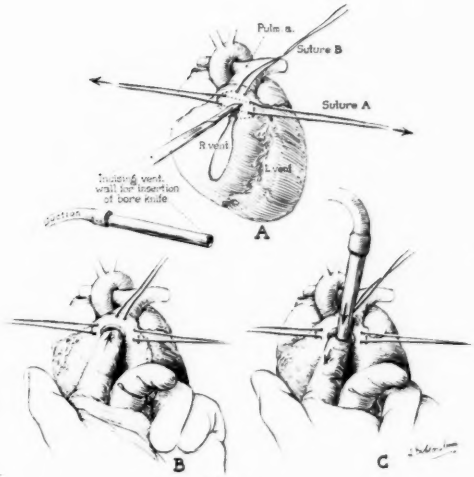


Fig. 2.

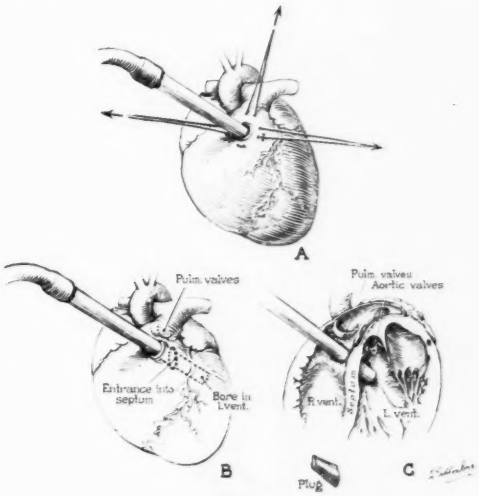


Fig. 3.

Fig. 2. Method of production of an interventricular septal defect. A, Mattress and pursestring sutures have been placed immediately beneath the pulmonary valves and an incision is made into the right ventricle while the mattress suture is held taut. B, The left index finger is inserted and the interventricular septum is palpated. C, The instrument is advanced as the finger is removed.

Fig. 3. A, As the instrument is introduced the pursestring suture is pulled taut. B, The cardiotome is advanced until it engages the septum and the suction is turned on. C, With a rotary motion the instrument is advanced through the septum. The cardiotome is removed along with the plug which it contains. The left index finger is then placed into the right ventricle and dilates the defect. The finger is removed and the mattress and pursestring sutures are tied. The insert reveals the configuration of the plug of septal tissue which was removed.

septum but also the anterior wall of both ventricles.

Two dogs died or were sacrificed on the seventy-sixth and seventy-eighth postoperative days. Both had excellent murmurs and thrills. They had ascites, 4 plus pitting edema of the hind legs, dilatation of the right and left ventricle, and pulmonary edema. The defects easily admitted the instrument ⅜ inch in diameter and were completely endothelialized (Fig. 4).

The remaining 11 dogs had murmurs and 5 had thrills at the time they were studied 7 to 13 months after production of the defects. Three of these dogs died between the seventh and thirteenth months following various investigative procedures; these 3 had patent defects. In 2 of these the defects were approximately the same sizes as when they had been produced, and in the third the defect had decreased to 5 millimeters in diameter. The defects, in addition, were completely endothelialized.

Cardiac catheterization pressures, oxygen content studies of blood samples taken from the femoral artery and cardiac chambers, systemic and pulmonary artery flow, as well as the presence or absence of a precordial thrill and murmur are tabulated in Table I. These dogs had a left to right shunt of 8 to 49 per cent. Seven of the dogs had shunts of 30 to 49 per cent 7½ to 12 months following the production of the interventricular septal defect. The dogs studied revealed a right ventricular hypertension. In 6 dogs the right ventricular systolic pressure was 50 millimeters of mercury or higher, and in 1 dog it was 100 millimeters of mercury. The pulmonary artery pressure was also slightly elevated in these animals but not as much as the right ventricular pressure. All of the pulmonary artery systolic pressures were 30 millimeters of mercury or above and in 4 dogs it was 38 millimeters of mercury or higher. In 17 dogs preoperatively the average pulmonary artery systolic pressure was 25 millimeters of mercury, and the average sys-

TABLE I.—DATA ON DOGS 7½ TO 12 MONTHS AFTER PRODUCTION OF INTERVENTRICULAR SEPTAL DEFECT WITH INSTRUMENT ⅜ INCH (9.3 MM.) IN DIAMETER

Dog No.	VK5	VK8	VK9*	VK11*		VK16†		VK23‡	VK24		VK25†	VK3
Weight, kgm.	21.0	18.3	15.0	19.0		13.6		17.5	22.8		25.4	22.(
Days between production of defect and study	306	319	369	305	370	299	354	232	238	285	273	286
Blood pressures, mm. of mercury												
Pulmonary artery	40/10	30/15	30/12	30/12	32/12	30/12	30/10	60/35	45/20	40/20	30/15	38/1
Mid right ventricle	50/0	40/0	38/0	50/0	75/0	35/0	45/0	100/0	65/0	55/0	50/0	60/(
Right auricle	5/0	5/0	10/0	10/0	14/5	10/0		15/5	15/0	16/0	16/0	5/(
Femoral artery	138/85	110/70		114/80		150/85		150/90	170/120		130/90	115/7
Femoral artery O_2 content, vols. per cent	14.42	15.8	18.28	14.24	19.78	14.11	16.20	13.10	15.76	18.14	21.48	20.2
Femoral artery O_2 saturations, per cent	88.4	76.3	88.7	78.2	92.6	84.2	89.0	86.2	79.8	84.8	89.2	90.1
O_2 A-V diff., vols. per cent Femoral artery minus pulmonary artery	4.2	2.25	1.53	1.86	1.92	2.96	4.89	2.80	2.78	3.59	3.77	2.30
Femoral artery minus right ventricle	6.0	4.43	2.73	3.46	3.46	3.34	5.33	4.06	3.90	4.39	5.54	3.86
O_2 uptake, ml. per min.	92	71	55	77	75	69	80	95	92		72	83
Pulmonary artery flow ml. per min.	2195	3155	3595	4140	3910	2330	1635	3395	3308	2565	1905	3605
Systemic flow, ml. per min.	1535	1602	2015	2225	2165	2065	1500	2340	2358	2095	1302	2150
Shunt, ml. per min.	660	1553	1580	1915	1745	265	135	1055	950	470	603	1455
Per cent of pulmonary artery flow due to shunt	30.0	49.3	43.9	46.4	44.6	11.35	8.3	31.5	28.7	18.3	31.6	40.4
Murmur	Fair	Fair	Good	Good	Good	Fair	Fair	Good	Good	Fair	Good	Good
Precordial thrill	None	None	Good	Good	Good	None	None	Good	Good	None	Good	None
Catheterization anesthesia	Pento-barbital	Pento-barbital	Pento-barbital	Pento-barbital	Mor-phine sulfate	Pento-barbital	Pento-barbital	Pento-barbital	Pento-barbital	Pento-barbital	Pento-barbital	Mor-phine sulfate

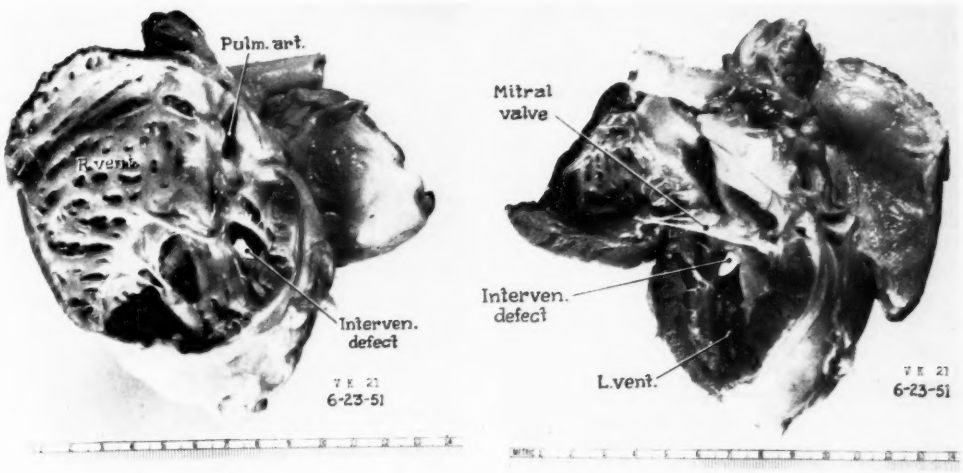
*No right to left shunt could be demonstrated by angiocardiography.
†Ventricular fibrillation occurred during cardiac catheterization and electrical defibrillation was employed with complete recovery. These studies were performed subsequently.
‡Congestive failure with moderate to marked ascites had been present 1 week prior to catheterization.

tolic pressure in the right ventricle was 30 millimeters of mercury. None of the experimental animals revealed any evidence of a right to left shunt, and angiocardiography in 2 of the animals with large shunts from left to right failed to reveal any evidence of a shunt in the opposite direction.

In 11 dogs with patent defects an exploratory thoracotomy was performed between the fourth and eighth months after producing the interventricular septal defect and a section of lung was removed for biopsy. These were examined histologically with particular reference to blood vessels. The smaller arteries, which lie adjacent to terminal bronchioles, revealed no evidence of intimal proliferation or medial muscular hypertrophy. The adventitia of these vessels was normal. The tiny vessels lying in the pulmonary parenchyma, in the walls of the alveoli and air sacs, did not show any changes. There was no microscopic evidence of enlargement of the bronchial arteries.

Microscopic examination of the tissue surrounding the defect in the animals that died or were sacrificed revealed the wall of the defect to be smooth and lined by endothelium. Immediately beneath this there was an orderly proliferation of endocardium and between these cells there was an accumulation of extracellular fluid. Beneath the layer of proliferating endocardium was a thick layer of hyaline fibrous scar and flecks of unorganized fibrin. Rare hemosiderin laden macrophages were present (Fig. 5).

The dogs which were sedated with 16 to 32 milligrams of morphine sulfate revealed fem-



. 4. Interventricular septal defect produced with .3 millimeter instrument. The animal was sacri- 5 days later because of cardiac failure. A, View of the right ventricle showing the large patent defect beneath the pulmonary valves. B, View of the left ventricle showing the large patent defect.

artery oxygen saturations of 90 and 93 cent, and those anesthetized with 15 to 20 ligrams of sodium pentobarbital per kilo- am body weight prior to study revealed moral artery oxygen saturations ranging om 72 to 89 per cent. These results are imilar to the femoral artery oxygen satura- ions obtained in control animals which were edated or anesthetized. As stated previously, ngiocardiography was performed in 2 of the logs with large left to right shunts, and no evidence of a right to left shunt was observed in these animals.

DISCUSSION

We were interested in producing interventricular septal defects of uniform size and shape and in studying the pathologic and physiologic changes that occur. The method described in this paper is the only reported method of producing a high interventricular septal defect resembling congenital defects

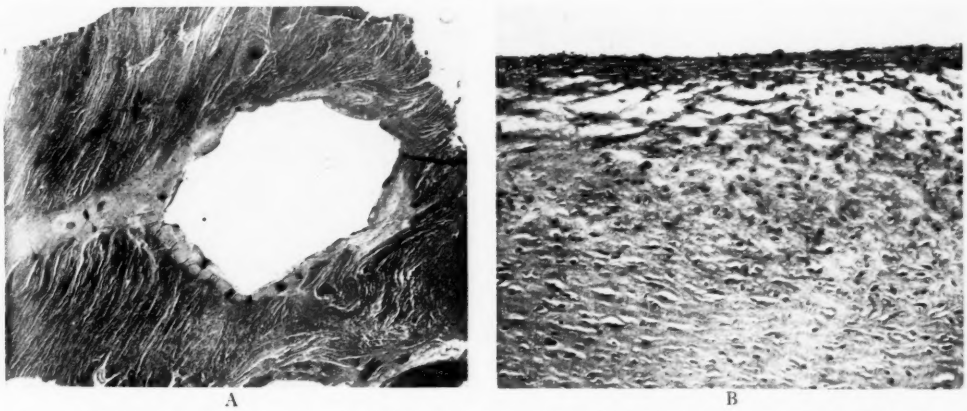


Fig. 5. Photomicrographs of walls of defect of Figure 4 showing endothelial lining. A, Low power. B, High power.

which remain patent over long intervals. Holman and Beck produced defects near the midportion of the septum with a cardiotome. Four of 10 of their dogs lived 7 weeks to 8 months with patent interventricular septal defects. Griffin and Essex produced interventricular septal defects; however, all of these defects closed spontaneously within 4 months. The defects produced by Griffin and Essex appeared to be placed lower in the septum than the defects described here and this position may be a contributing factor in the closure of their defects. In our series of 35 experiments 19 animals survived the immediate postoperative period and in only 3 of these was there evidence of closure of the defect. In the remaining 16 animals the defects were patent 6 weeks to 13 months later.

Nine of these animals were studied 7½ to 12 months after production of the defect. These animals revealed a slight to moderate rise in the right ventricular pressures associated with either a less pronounced rise or no rise in the pulmonary artery pressures. The average right ventricular systolic pressure in our control dogs was 30 millimeters of mercury, and the average pulmonary artery systolic pressure was 25 millimeters of mercury. In the experimental animals the ventricular systolic pressure in 6 of the 9 dogs studied was 50 millimeters of mercury or higher.

In 5 dogs in which Griffin and Essex produced interventricular septal defects 10 millimeters in diameter, there was a 43 to 83 per cent left to right shunt immediately after the operation. Eppinger and Gross produced interventricular septal defects 4 to 6 millimeters in diameter in 5 dogs and measured the amount of shunt in the immediate postoperative period. Thirty to 50 per cent of the output of the left ventricle was shunted into the right ventricle. In our chronic experiments the left to right shunt was determined 7½ to 12 months following the production of the defects and was found to vary from 8 to 49 per cent of the left ventricular output. Seven of the dogs had shunts greater than 30 per cent.

In our animals as well as in those of Griffin and Essex, there was no evidence of a right to left shunt. Angiocardiograms on 2 animals failed to reveal a shunt in this direction and femoral artery oxygen saturations were the same as in control dogs which were sedated by morphine or anesthetized by sodium pentobarbital. Penrod and Hegnauer reported similar lowering of the oxygen content of normal dogs with pentothal sodium injection. Our experimental results would probably be of greater significance if we had used lighter anesthesia. However, interestingly enough, the 2 dogs which were sedated with morphine and atropine had shunts greater than 40 per cent.

In 11 dogs with patent defects an exploratory thoracotomy was performed between the fourth and eighth months after producing the interventricular septal defect and a section of lung was removed for biopsy. Histologically there was no evidence of vascular changes noted in these sections even though the defect was large enough to produce congestive failure in some of the animals. It must be remembered, however, that these animals are not subjected to strain and exercise and there might be alterations in the pulmonary vessels if this were allowed. The time interval between the production of the defects and removal of sections of lung for biopsy is also most likely not long enough to allow changes in the pulmonary vascular system even though these are chronic experiments. Some of these animals will therefore be studied at a later date.

SUMMARY

A patent high interventricular septal defect of a known size can be made by applying pressure and suction to a sharp steel instrument of the design of a cork borer. Fifty-nine per cent of the animals survived the immediate postoperative period and the defects remained patent in approximately 84 per cent of these animals. Cardiac catheterization was performed 7 or more months after production of the defect, and there was a shunt of blood from left to right amounting to 8 to 49 per cent of the total pulmonary blood flow. Angiocardiography and studies of the femoral artery oxygen content did not indicate a right to left shunt. The animals revealed a slight to moderate right ventricular hypertension and an even smaller rise in pressure in the pul-

monary artery. The defects were so large that some of the dogs died of congestive failure, but, despite this, there was no evidence of macroscopic or microscopic changes in the pulmonary vascular tree.

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THE FATE OF RECURRENT OR PERSISTENT PAROTID TUMORS

DANELY P. SLAUGHTER, M.D., F.A.C.S., HARRY W. SOUTHWICK, M.D., Chicago, Illinois, and LEROY WALTER, M.D., Glendale, California

ALTHOUGH a number of excellent reviews of parotid tumors have been published recently, it has seemed worth while to present our material this subject in order to emphasize three ordinal points. These points are: (1) the variety of pathologic conditions that can occur in the parotid gland aside from acute inflammatory swellings and obstruction; (2) the incidence of cancer; and (3) the possibility of malignant transformation of benign mixed tumors.

Two hundred and twelve patients with tumors of the parotid gland have been studied. The pathologic material has been reviewed, and the main diagnostic headings and percentage incidence are listed in Table I. It will be seen that the benign mixed tumors comprise almost 60 per cent of the total, but that malignant tumors constitute 26 per cent. Almost 15 per cent of the parotid swellings investigated surgically in this series are benign lesions not classified as mixed tumors.

VARIATIONS

Twenty-three separate diagnostic headings are listed in Tables I, II, and III. This bewildering variety of lesions explains some of the diagnostic difficulties inherent in both the clinical and pathologic definition of parotid tumors. Detailed classifications, however, are mainly of academic import and these tables are presented not as a new classification, but simply as an example of our experience and the interpretation thereof. The broad facts, that nearly one-third of the mixed tumors were recurrent after surgery when we first saw the patients and that 1 in 4 of the parotid tumors was malignant, are of immediate clinical interest. Within the mixed tumor group itself there are marked differences in histologic pattern and divergence in the microscopic estimates of growth potential. Because of this we have classified as cancer only those tumors with both clinical and pathologic evidence of malignant behavior. Tumors described as "mixed tumor, highly cellular, possibly malignant," or by other equivocal phraseology have been considered to be benign "mixed tumors." This may partially explain the discrepancy between Buxton's figures of 104 malignant neoplasms in a series of 227 parotid tumors and our figures of 26 per cent. Yet, this borderline group of debatable tumors may have clinical significance, there being many shades of gray between black and white.

In this connection, it may be observed that 36 of our benign mixed tumors were recurrent

From the Department of Surgery, University of Illinois College of Medicine, Chicago, Illinois.

TABLE I.—PAROTID TUMORS

	No. cases	Per cent
Mixed tumors	124	59.2
Primary....88		
Recurrent....36		
Malignant tumors	55	26.0
Miscellaneous pathology	23	10.4
Warthin's tumors	10	4.4
Total	212	

or persistent when first seen by us, after excisional surgery elsewhere. When original slides were available, comparison with the recurrent tumor revealed in the majority of instances no change in tumor type. These recurrent tumors were essentially of the ordinary or "average" mixed tumor type, without marked cellularity and with relatively abundant myxomatous stroma and occasional "cartilaginous" areas. In contrast to this, in the malignant tumor group there are 12 parotid cancers which can reasonably be considered to have originated from pre-existing mixed tumors. In 8 instances prior excisional material was available for study and in all cases revealed the original tumor to be highly cellular, of unusual cell pattern, or with suggestively atypical cell type. Some were adenomatous in character and all showed minimal myxoid elements. None of them, in our opinion, justified an original diagnosis of cancer either on clinical or pathologic grounds. It is our impression that recurrence was due to incomplete excision in the first place, and that the growth characteristics of the residual tumor changed, becoming manifest as cancer in our subsequent surgical material. Four of these were adenocarcinomas retaining enough cell pattern to allow definition as malignant mixed tumors. From the foregoing considerations we have concluded that the group of equivocal or atypical mixed tumors has separate clinical import, with a direct bearing on the type of surgical approach used.

TABLE II.—MALIGNANT TUMORS (26 PER CENT)

	No. cases
Adenocarcinoma	27
Mucoepidermoid carcinoma	8
Epidermoid carcinoma	6
Adenoid cystic carcinoma	4
Small round cell carcinoma	2
Papillary adenocarcinoma	2
Papillary cystadenocarcinoma	2
Lymphosarcoma	1
Endothelioma	1
Teratoma with embryonal carcinoma	1
Chondromyxosarcoma	1
Total	55

INCIDENCE OF PAROTID CANCER

The incidence of malignant parotid tumors in published series varies with the generosity or critical discrimination of the pathologist's interpretation. The reported percentages vary from nearly 50 per cent to around 15 per cent. The consensus, however, varies from 17 to 25 per cent. Our incidence in this series is 26 per cent. This may in very small part be explained by selective referral of advanced and hopeless cases to the tumor clinic of a university teaching hospital. In any event, whether 1 in 4 or 1 in 5 of surgical parotid swellings is cancer, the fact remains that any lump in the parotid gland has grave clinical potential. This is well known to all students of the problem, but it is not generally appreciated by the profession. The diagnosis may be obvious in advanced cases or in earlier lesions with facial nerve paresis, but many potentially curable parotid cancers may be missed by the surgeon inept in surgical pathology, the actual diagnosis being returned as a surprise some days later. Because of these aspects, some modification of our attitude and surgical approach to parotid tumors is in order.

MALIGNANT TRANSFORMATION OF PREVIOUSLY BENIGN PAROTID TUMORS

In our group of 55 patients with parotid cancer, there are 12 malignant tumors whose origin can be traced with reasonable certainty

TABLE III.—MISCELLANEOUS PATHOLOGY (10.4 PER CENT)

	No. cases
Granuloma	8
Cyst	6
Tuberculosis	2
Boeck's sarcoid	1
Lymphangioma	1
Lipoma	1
Hemangioma	1
Adenoma	1
Parotitis	1
Lymphoid hyperplasia	1
Total	23

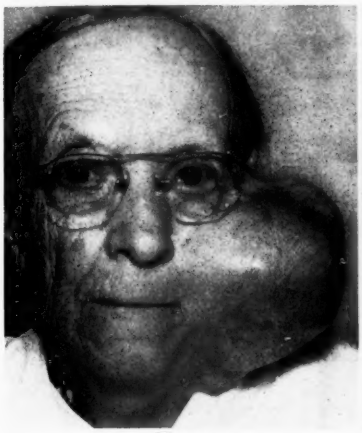

Fig. 1.

Fig. 2.

Figs. 1 and 2. Preoperative and postoperative pictures of an 84 year old woman with untreated parotid tumor of over 40 years' duration. In the preceding 10 months the lesion had assumed rapid growth from the size of a lemon to the present state. Complete left facial paralysis and severe pain indicated malignant transformation, and a palliative excision was performed under local anesthesia. The tumor was a mixed spindle cell and chondrosarcoma.

pre-existing benign tumors. Two of these tients had never had previous surgery, even psy, but both had parotid tumors of 41 and years' duration, respectively. These tu- rs had slowly enlarged during this time, h long stationary periods, and each experi- ed very rapid growth with pain, facial ve paralysis, and metastases in the 6 to 10 nths preceding our observation. One of se patients, a female aged 78 years, had y a neck node removed for biopsy purposes, primary lesion being completely inoper- ble. The node was replaced by an anaplastic carcinoma which, nevertheless, was of salivary gland type and was vaguely reminiscent of a mixed tumor. The other patient (Fig. 1) was a female, aged 84 years, whose tumor was of 45 years' duration, which likewise had grown only slowly and to moderate size during that time, until its recent rapid enlargement. Because of pain the tumor was removed under local anesthesia in spite of pulmonary metastases (Fig. 2). She lived 2 more years and expired without local recurrence. The tumor was a mixed spindle cell and chondrosarcoma, without discernible epithelial elements.

Two other patients with massive carcinomas of the parotid are of particular interest. One (H. J.) was a male, aged 45 years, first seen by us in 1946 (Fig. 3). His first parotid tumor excision was performed in 1935 for a small tumor said to be of 5 years' duration. This was reported as benign mixed tumor. It recurred and was again excised in 1938, being reported as mixed tumor. The lesion recurred in 1940, was excised, and then reported as possibly malignant. It recurred promptly and in the next few years was subjected to multiple excisions and numerous exposures to x-ray and radium therapy as a declared cancer. When first seen in the Tumor Clinic of the Illinois Research Hospital (Fig. 3), the lesion was not considered operable until one of the student clerks pointed out that the man's facial nerve was completely intact in all its branches. Excision and neck dissection for positive nodes were then performed, and, finally, the facial nerve was sacrificed (Fig. 4). The patient remained well 4½ years, except for 2 small local recurrences, and then succumbed rapidly to cerebral metastases.

The second patient with massive disease (Fig 5) was a male, aged 74 years, whose parotid tumor originated in 1903. It had been excised in 1910 and again in 1923. According to the patient the tumor was reported as benign

Fig. 3.

Fig. 4.

Figs. 3 and 4. Preoperative and postoperative views of a 45 year old male with parotid tumor of 16 years' duration. Originally benign, after repeated recurrence and incomplete excision this picture was presented. Intact facial nerve indicated attempt at excision. This was accomplished along with radical neck dissection and, of course, sacrifice of the seventh nerve.

on each occasion, but he also stated that he thought it had not been completely removed either time. Since 1923, the residual mass slowly enlarged and finally attained the size of a lemon externally. In September, 1948, it suddenly began to enlarge rapidly and by May of 1949 presented the appearance shown in Figure 5. Cervical node metastases were extensive but not fixed, and there was roentgen evidence of invasion of the angle of the mandible. Again to our surprise the facial nerve was intact except for weakness of the mandibular branch. Because of this, excision was attempted and successfully completed after radical neck dissection and removal of the right hemimandible. The facial nerve was of course sacrificed, and a split thickness graft was placed over the external surface of the exposed buccal mucosa. The appearance on the tenth postoperative day is illustrated in Figure 6. The tumor was a mixed "carcinosarcoma" suggestive of mixed tumor origin. The patient lived in good health for 2½ years and then rapidly succumbed in a few weeks' time with pulmonary and hepatic metastases, but without local recurrence. Of the other 8 patients, 3 had only 1 previous excision showing mixed tumor, and the later malignant lesion was diagnosed at intervals of 4 years, 5 years, and 10 years, respectively. The other 5 all had multiple excisions over periods of many years before the malignant clinical and histologic picture supervened. In 4 of these the pathologic material has been verified, and in the other the institution where the original excisions were performed presented an unquestioned description of a benign mixed tumor.

SURGICAL APPROACH TO PAROTID TUMORS

The rare lymphosarcomas and an occasional hemangioma in the parotid gland may be indications for radiation therapy, but even these lesions require surgical exploration for diagnosis. All other parotid tumors are surgical problems, radiation being of only adjunct or palliative value.

It is not the purpose of this paper to outline details of surgical technique, as this has been done completely by Hamilton Bailey, David State, J. B. Brown, Hendricks, Byars, and others. We are in agreement with the modern concept that no benign parotid tumor should be enucleated, but that either a superficial lobectomy or total parotidectomy is the minimal justifiable procedure. Such an operation requires identification of the facial nerve branches, a relatively easy maneuver for the operator experienced in this field. It is our experience that descriptions of methods for locating the nerve that are based on cadaver dissections have little or no relationship to the nerve displaced in any of three planes by the presence of a tumor.

Superficial lobectomy should suffice for the majority of mixed tumors of the parotid. Total parotidectomy is occasionally indicated for

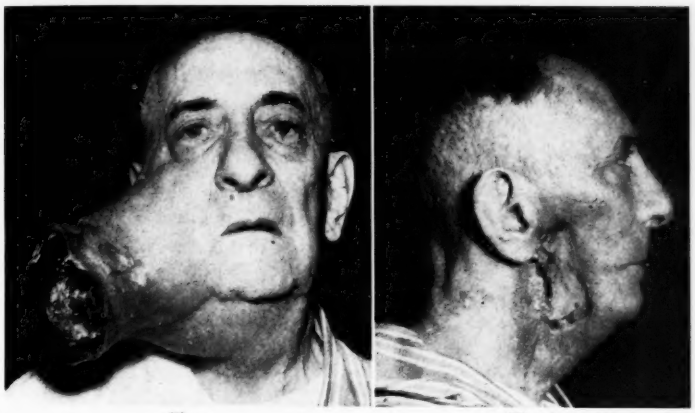

Fig. 5. Fig. 6.

Figs. 5 and 6. Preoperative and postoperative views of a 74 year old man with parotid tumor of 46 years' duration. It had remained quiescent for 20 years after 2 incomplete excisions. Rapid growth then occurred and in 9 months it attained the present size. The mandible was invaded and cervical node metastases were obvious, but the main trunk of the facial nerve was intact, indicating potential resectability. This was accomplished along with radical neck dissection and excision of the hemimandible.

mors of the deep lobe, but we do not believe is procedure should be employed routinely all parotid tumors. To our mind, the so far proved benefits of routine total excision are tweighed by the danger of permanent facial ve damage, with its attendant psychologic d even financial harm to the patient. We e referring, of course, only to benign tumors. The surgical treatment of cancer of the rotid is an entirely different matter. Since nically innocent lesions have such a dangerous statistical possibility of being actually malignant, every parotid tumor should be identified insofar as possible before the patient leaves the operating room. This means that the surgeon and pathologist should cut the specimen and examine frozen sections on all tumors at once. Admittedly the gross and microscopic definition is more difficult than in breast tumors, but a sincere and responsible attempt should nevertheless be made.

If an infiltrating malignant tumor is diagnosed without question, then a total parotidectomy should be performed, with sacrifice of the facial nerve and any other adjacent tissues that may be involved. Temporizing with a definite parotid cancer is homicide, and the facial nerve must be considered as condemned tissue. If the surgeon does not take it, the tumor will, and the rest of the patient along with it. It is only very rarely justifiable to preserve the nerve, and the authors have only done it in a few instances of extremely small infiltrating cancers located in the tail of the parotid or very superficially under the external parotid fascia.

When cervical node metastases are present a radical neck dissection should be done in continuity with the parotid excision. It is possible that this should be done routinely for parotid carcinomas, but statistical evidence to support this is not available. Neck dissection adds little in operative time, risk, or disability.

DISCUSSION

The majority of parotid tumors are benign, but the incidence of cancer is higher than is generally appreciated. Mixed tumors will all recur if incompletely removed, but most of them retain their original microscopic structure. If allowed to persist over many years, malignant transformation may occur, but it is our impression that this is more likely to occur in the group of mixed tumors that are atypical, unusually cellular, and whose diagnosis is equivocal. In our 12 cases of parotid cancer

which we consider to have originated from benign mixed tumors, the available prior histology is atypical but benign. In the 2 cases in which clinically benign tumor persisted for more than 40 years before cancer supervened, it would seem to be sophistic quibbling to consider them cancer from the beginning. It is probable that complete excision at any time in their benign course would have eliminated the fatal termination as cancer.

CONCLUSIONS

1. Two hundred and twelve cases of parotid tumor have been reviewed. Sixty per cent of these were benign mixed tumors, of which one-third were recurrent when first seen by us.

2. Recurrent or persistent mixed tumors may become malignant in time, and in this series there were 12 cancers out of a total of 55 which we believe originated from pre-existing benign tumors.

3. It is our impression that malignant transformation is more likely to occur in the cellular and somewhat atypical mixed tumor group.

4. The incidence of actual cancer of the parotid gland is at least 20 per cent or 1 tumor in 5, and in our series it is 26 per cent.

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HYPERCHLOREMIC ACIDOSIS

A Study of the Mechanism in Ureterosigmoidostomy

A. WAITE BOHNE, M.D., and C. E. RUPE, M.D., Detroit, Michigan

THE increasing possibilities for adequate radical surgery in carcinoma of the urinary bladder have uncovered an interesting problem in bowel physiology and electrolyte metabolism. Ureterosigmoidostomy is followed in a large proportion of cases by hyperchloremic acidosis. Improvement in control of this complication depends on a more precise understanding of the mechanism of its production. The current hypotheses are of two varieties: (1) reabsorption of urinary chloride by the sigmoid mucosa and (2) renal damage incident to infection and obstruction producing functional derangement.

The blood electrolyte picture in the acidosis seen after ureterosigmoidostomy reproduces that of excessive ingestion of ammonium chloride (15 grams per day) in individuals with normal kidney function. To test the validity of the hypothesis that chloride absorption is the mechanism of acidosis when urine is diverted into the sigmoid we may assume the presence of acidosis to indicate the absorption of 15 grams of ammonium chloride or its equivalent and in this way express the volume of reabsorbed urine necessary to deliver this chloride load:

$$\frac{\text{volume of urine excreted}}{\text{volume of urine formed}} = \frac{\text{ammonia produced} - \text{ammonia reabsorbed}}{\text{ammonia produced}}$$

For example: In a patient with ureterosigmoidostomies in water balance with an intake of 3,000 milliliters, an insensible loss of 1,500 milliliters and a urinary output of 1,500 milliliters from the sigmoid pouch, let us assume normal kidney function which places the ammonia producing capacity at 16 to 26 grams of ammonium chloride per day (Fig. 1). At the upper limit of normal the amount of urine reabsorbed per 24 hours to supply an acidosis producing chloride load (15 grams per day) would be:

$$\frac{1500}{1500 + x} = \frac{26 - 15}{26}$$

$$x = 2{,}000 \text{ ml.}$$

At the lower limit of normal (16 grams per day) a seemingly impossible volume of 22,500 milliliters a day would have to be reabsorbed to produce acidosis on this basis.

This preliminary examination of the reabsorption hypothesis, while not considering differential rates of water and chloride absorption, led to the consideration of sources of other than preformed ammonia. The obvious possibility of bacterial decomposition of urea to ammonia would seem to be essential initiation of the acidosis as well as an important factor in its perpetuation. Boyce and Vest have reported this additional source to be of practical significance in one of their patients in whom control of urea splitting organisms was helpful in therapy. A forceful reminder of the degree of urea to ammonia conversion is the observation of alkaline urine issuing from the "sigmoid bladder" of a patient in severe acidosis.

METHODS

In order to study the behavior of the sigmoid mucosa toward urinary electrolytes an instrument was devised on the suggestion of Dr. George Mangun with which a sealed section of bowel could be obtained in the intact animal (Fig. 2). Under sodium nembutal anesthesia, adult mongrel dogs could be used for repeated observations by inserting the instrument, securing a seal by applying suction, irrigating the sealed segment, instilling the solution to be studied, and withdrawing aliquots at regular intervals. A large rubber stopper served to seal the anus. In 2 patients with double-barreled colostomies large bag Foley catheters were used to seal the anal and

From the Division of Urology and the Department of Medicine, Henry Ford Hospital, Detroit.

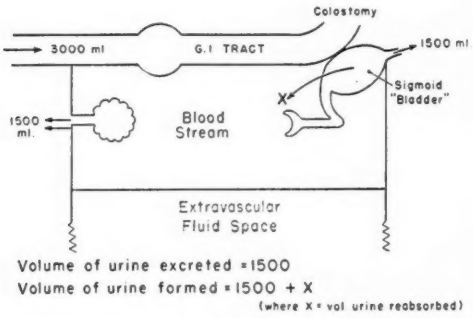

Fig. 1.

Fig. 2. Instrument by which a sealed section of bowel may be obtained in the intact animal.

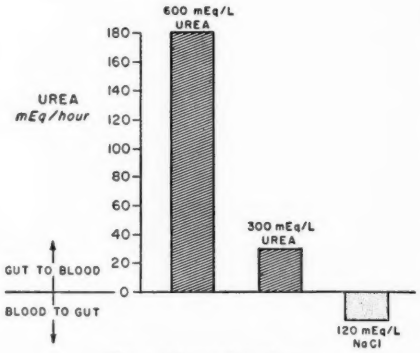

Fig. 3. Absorption of urea.

abdominal ends of the defunctioned sigmoid. In another patient retransplant of the ureters back to the bladder gave opportunity to study the sigmoid bladder before the bowel was reanastomosed. Solutions of urea, ammonium chloride, sodium chloride, mixtures of sodium and ammonium chloride, and each of these plus disodium phosphate were studied in concentrations at, above, and below isotonicity. After instillation of 100 milliliters of these solutions aliquots of 10 milliliters were withdrawn every 15 minutes for 1 hour and analyzed. An attempt was made to mark changes in water volume in various ways; phenolsulfonphthalein was the only satisfactory means found.

Urea solutions instilled into the sigmoid gave evidence of varying degrees of urea breakdown. Absorption from hypertonic solutions was significant in amount while from hypotonic and isotonic solutions little absorption was apparent (Fig. 3). Movement of urea from blood to gut was demonstrated. The rates of urea breakdown versus absorption are not discernible without resorting to tagged urea since the ammonia formed and absorbed as such would appear in the calculation as absorbed urea. The speed of action of urease at body temperature would suggest that ammonia formation would begin earlier and proceed more rapidly than simple diffusion of urea from gut to blood.

The effect of phosphate in the solution instilled into the sigmoid on the rate of chloride absorption is seen in Figure 4. This enhancement of the absorption of univalent ions by a divalent ion of the same charge was first studied by Goldschmidt. Our study suggests that the buffering capacity is the mechanism by which phosphate allows more rapid and complete absorption across the sigmoid mucosa. Comparing rates of chloride absorption from sodium chloride and ammonium chloride again suggests that the defense of the hydrogen ion concentration plays a part in determining the speed and direction of ion movement across the sigmoid mucosa.

The nature of the secretion absorption mechanisms of the intestine has been relatively obscure until recent years because of the inherent difficulty in assessing movements of specific ions and water into and out of the gut simultaneously. Until the excellent work of Visscher and associates only net changes in concentration could be appreciated. Application of isotope technique to the problem allowed precise measurement of both water and ion movement between the gut lumen and the blood stream. It became evident that the use of osmotic gradients and comparisons of concentrations of a particular ion on either side of the mucosa of the sigmoid were not usable in explaining the observations on absorptive function. It was shown by Visscher

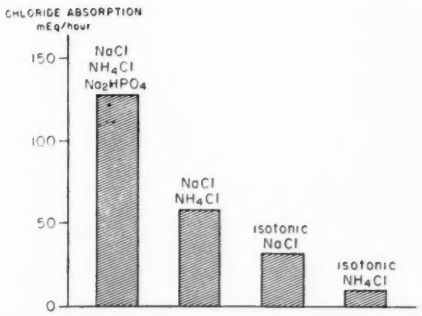

Fig. 4. Influence of phosphate ion on chloride absorption.

that the intestine accomplishes the transportation of ions against a concentration gradient by means of a "forced flow" in a biologic fluid circuit. Application of these findings in a study of ileal loops to the problem of absorption of urinary constituents from the sigmoid reveals: water may move from hypertonic urine to blood; chloride moves in both directions, the movement into the gut being relatively constant and independent of the tonicity of the solution in the gut; the rate of absorption of chloride is influenced by the presence of other ions.

Without isotopic marking to make evident water movement and the simultaneous bidirectional ion movements demonstrable, only the net change can be determined. By marking the volume of solution in the sigmoid with a nonabsorbable dye (P.S.P.) we have been able to correct the net concentrations observed for the dilution or concentration due to water gain or loss. No correction could be made in this study for any of the blood constituents which moved into the gut lumen unless the solution were devoid of that constituent at the outset. The demonstrated net rates of water and ion movements in this study of the sigmoid colon in dogs and humans show an enhanced movement of chloride due to the presence of phosphate, increasing in speed with the movement of sodium into the lumen and possibly increased further as additional ammonia is formed from the breakdown of urea.

Since the absorption of chloride across the bowel mucosa is established, the presence of

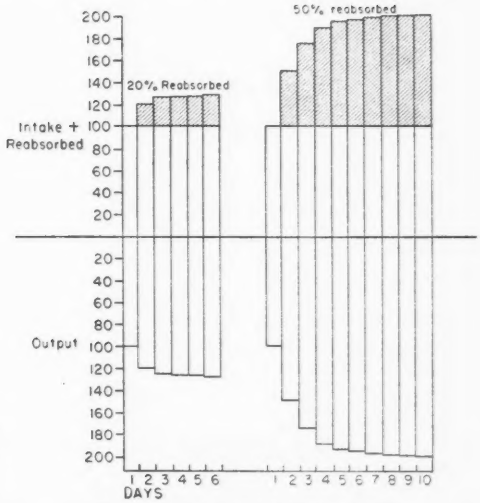

Fig. 5. Hypothetical chloride balance.

hyperchloremic acidosis in a patient with ureterosigmoidostomy indicates that chloride intake plus reabsorption has exceeded output; that a positive chloride balance is being enforced by the recycling of chloride. If chloride absorption were complete in the sigmoid as it is in the small bowel, the accumulation of chloride would become a summation of each day's intake less the minor amounts lost in the sweat and feces. On the other hand, if the sigmoid mucosa were impermeable to chloride, no disturbance in chloride balance would occur. Between these extremes near balance may be attained and maintained for any given percentage reabsorption. This possibility is expressed in the following formula:

$$T = \frac{xy(1-y^n)}{1-y}$$

where x = intake, y = per cent reabsorbed and T = total remaining after n days. If the intake of chloride is 100 milliequivalents per day and 20 per cent is reabsorbed; over a period of 5 days only 26 milliequivalents will accumulate and over a period of a hundred days at the same intake, no further accumulation would occur (Fig. 5). This relationship is based on the supposition that the percentage reabsorbed will remain constant; however, the

data reported here indicate that the increasing load for excretion would raise the amount reabsorbed *unless* concentration remained at the same level by increased water excretion.

The role of the kidney in the acidosis of ureterosigmoidostomy has received a great deal of attention and is still held by some to be the primary feature in pathologic physiology. The frequent clinical observation of reversal of the acidosis by rectal tube drainage is a damaging piece of evidence against this concept. The high level of serum chloride characteristic of the acidosis after diversion of urine to the sigmoid is not the expected blood electrolyte picture in primary renal acidosis. Greatly elevated serum chloride levels are seen with near normal nonprotein nitrogens. Mitchell and Valk found no correlation between the presence of acidosis and detectable renal functional impairment. We have had the unusual opportunity during this study to observe a patient whose ureters had been transplanted to the sigmoid to control incontinence and in whom plastic repair brought return of continence and permitted transplant back to the bladder. A marked chloride diuresis occurred immediately postoperatively and serum chloride levels fell from the preoperative level of 124 to 96 milliequivalents per liter in 96 hours, requiring potassium chloride and ammonium chloride therapy to return chloride levels to normal.

There remains to explain the occasional patient who does not go into acidosis following ureterosigmoidostomy. Frequency of emptying the sigmoid of urine and voluntary low chloride and high water intake have been considered sufficient explanation for all cases without acidosis in one series. The nature of the mucosa in the rectosigmoid and the mechanics of flow over the mucosa may be a factor. The changeability of absorptive function noted by Visscher and Carr and the marked change in appearance of the sigmoid mucosa after prolonged exposure to urine suggest some adaptability of function. Another adaptive possibility would make use of the decreased rate of chloride absorption in the absence of phosphate by means of habitually lower intake or alteration in parathyroid function.

The extreme chloride diuresis seen in the patient whose transplants were "taken down" suggests an adaptive capacity on the part of the tubules in the direction of allowing excretion of more chloride rather than less as is indicated by those who hold the kidney responsible for the hyperchloremic acidosis seen in ureterosigmoidostomy. Also, as shown by the previous formula:

$$T = \frac{xy(1-y^n)}{1-y}$$

balance may be attained and maintained until such time as a serious illness, diarrhea, or voluntary dehydration disturbs this balance, thus permitting the recycling to proceed. Thus some patients who can maintain balance may never develop the hyperchloremia.

SUMMARY

The mechanism of hyperchloremic acidosis in ureterosigmoidostomy has been examined from the standpoint of the absorption mechanism of the sigmoid mucosa. The rates of chloride absorption were influenced by concentration, the presence of phosphate, and apparently by the hydrogen ion concentration. Theoretic consideration of given absorption rates provides a basis for understanding the cases of patients who do not manifest acidosis and suggests that renal damage is not an essential feature in the pathologic physiology.

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A REVIEW OF THE EFFECTIVENESS OF EARLY TREATMENT IN BREAST CANCER

ARTHUR S. KRAUS, Albany, New York

IN AUGUST, 1951, an article by Park and Lees entitled "The Absolute Curability of Cancer of the Breast" was published. It has since been read widely and with great interest by clinicians, surgeons, and personnel engaged in cancer control programs and has exerted a strong influence on the thinking of these interested groups. In that article, the authors review the literature on breast cancer treatment, as well as an analysis of their own data, to conclude that treatment of breast cancer has been ineffective. In their own words, "The evidence strongly suggests that treatment is quite ineffectual in reducing the incidence of death from metastatic spread. If treatment is in any way effective, the effectiveness cannot be greater than that required to increase the overall 5 year survival rate by more than 5 to 10 per cent."

The purpose of the present review is to evaluate this conclusion. The material in the Park and Lees article will be primarily relied on for evidence, except that one other article published by Harrington since the appearance of the Park and Lees article will also be utilized.

Park and Lees approach the problem by estimating a maximum expectation of real curability of breast cancer by present methods of treatment. They then attempt to show that the true real curability is much less than the estimated maximum because factors other than treatment itself were contributing to the size of the maximum. These arguments will be discussed in detail.

Park and Lees make two estimates of the maximum expectation of curability on page 135 of their article. The first one, 25 per cent, was based on the difference between 5 year survivals in reported series of total cases, including treated and untreated, compared with the 5 year survivals in a reported series of untreated cases. Since the survivorship of a representative total study group may be decreased because some untreated cases are included, a greater and more logical estimate would be based on the difference between 5 year survivals for treated cases only, on the one hand, as compared with the 5 year survivals for untreated cases, on the other hand. But even this would not be adequate, since a representative treated series would at present contain many cases in which avoidable delays had occurred, and the maximum expectation of curability for present methods of treatment should be based on a comparison in which all the treated cases are treated at the earliest practically attainable time.

Park and Lees' second estimate of the maximum expectation of curability is based on the estimated difference in survivorship after radical mastectomy in cases treated without delay as compared with cases treated after a 3 year delay from onset of symptoms. The calculations assume 20 per cent 5 year survivorship for patients with breast cancer with axillary metastases at time of treatment and 70 per cent 5 year survivorship for those without such metastases. It is also assumed that 60 per cent of all patients with breast cancer have discoverable axillary metastases at the time of onset of symptoms, and that only 75 per cent would have such metastases if treatment were delayed 3 years after onset of symptoms. Both parts of this latter assumption are questionable. It is true that in Table II on page 145 of their article, approximately 60 per cent of the patients treated within 1 month after onset, and approximately 75 per cent of those treated after a 3 year delay, had axillary metastases. However, it is amply indicated in various quotes used by Park and Lees themselves that the patients with the more malignant types of cancer tend to come to treatment earlier, and that those cancers

From the Bureau of Cancer Control, New York State Department of Health, Albany, New York.

which are still treatable 3 years after onset tend to represent the lower degrees of malignancy. In Table II itself, only 52 per cent of the patients who were treated 3 to 4 months after onset had axillary metastases, and perhaps some of these could have been treated sooner with a possible lower incidence of metastases. Therefore, it seems very probable that the incidence of axillary metastases at the time of treatment for all cases of breast cancer would be well under 60 per cent if they were all treated at the earliest time attainable in practice. Furthermore, if no patients with breast cancer were treated until 3 years after onset, a good proportion would undoubtedly develop axillary metastases and die before this period was reached. *This group was completely ignored in the estimate of survivorship for the group treated after a 3 year delay from onset. Those remaining alive would have at least the 75 per cent axillary metastasis used by Park and Lees. Therefore, the incidence of metastasis for the entire breast cancer population during the 3 years after onset would be much greater than the 75 per cent that was assumed.*

The difference in estimated survivorship after onset of symptoms in the entire breast cancer population treated without delay as compared with the same group treated after a 3 year delay would thus be much greater than estimated by Park and Lees, and would more closely approximate a measure of the maximum curability by present methods of treatment.

There are several types of data involving clinical series of breast cancer cases which are commonly offered in support of the argument that treatment is effective in breast cancer, and that this effectiveness increases with earlier treatment. These are comparisons showing higher survivorship for treated groups than for untreated groups, higher survivorship for patients without axillary metastases at the time of radical mastectomy than for those with such metastases, higher survivorship for stage I cases than for cases of higher stage, and higher survivorship for patients treated after short duration of symptoms than for those treated after longer duration of symptoms. Park and Lees stress the importance of the variability of growth rates and of degree of intrinsic malignancy of breast cancers, and the need for interpreting all survivorship comparisons in the light of this variability. That viewpoint is accepted here. It is admitted that in the comparisons involving treated versus untreated cases, those without axillary metastases versus those with such metastases, and stage I cancers versus those of higher stage, the groups showing higher survivorship probably contain a higher proportion of intrinsically lower malignancies. This would account for an unknown part of the higher survivorship found, thus decreasing the amount of higher survivorship attributed to early treatment itself.

However, it would seem that the same criticism does not apply to comparisons showing higher survivorship for patients treated after a short duration of symptoms than for those treated after a longer duration of symptoms. Park and Lees give ample evidence that there actually is a tendency for the intrinsically higher malignancies to come to treatment sooner, so *that higher survivorship for cases of shorter duration in a total breast cancer study group cannot be due to the inclusion of an excessive proportion of intrinsically lower malignancies in that group.* It is apparently due to the gains in survivorship resulting from earlier treatment for a portion of the cases within each level of intrinsic malignancy. This is the same as saying that earlier treatment is effective.

McKinnon has criticized comparisons of survivorship for cases at different stages on the grounds that stage I cases will include a higher proportion who survive because theirs were benign cases that were misdiagnosed as cancer. Such a possibility undoubtedly exists, but it would appear that the problem of misdiagnosis does not bias comparisons of survivorship for patients with short or long duration of symptoms before treatment. If a truly noncancerous case will be misdiagnosed as cancer soon after the onset of symptoms, it would probably still be misdiagnosed if the patient delayed a while before seeking treatment, since the progression and development of symptoms which help remove doubt as duration increases in true cancers would not

occur in noncancers. Although truly malignant cancers will progress as duration increases, it seems doubtful that the timetable of malignancy is clearly enough defined to permit more correct diagnoses of noncancers as duration increases up to 2 or 3 years after onset of symptoms, merely on the basis of the difference between the noncancer and what a true cancer should be like at that duration. Therefore the proportion of false positive diagnoses of cancer in cases of shorter or longer duration of symptoms should be similar, and the difference in survivorship for the two groups should not be influenced by this factor.

In view of the above arguments, the figures quoted by Park and Lees relating survivorship to duration of symptoms before treatment impressively demonstrate the effectiveness of early treatment. The quote on page 138 from Eggers, de Cholnoky, and Jessup (1941) reports a gradual decrease in 5 year survivorship with increasing duration of symptoms, for a breast cancer group, from 76 per cent for patients whose operation was delayed for 1 month to 20 per cent for those whose operation was delayed 2 years. The summary of Geschickter's study (1947) on page 139 shows a decrease in 5 year survivorship from 80 per cent for patients with a 2 months' delay to 3 per cent for those with 18 months' delay in treatment among the patients with infiltrating breast cancers, and a decrease from 95 per cent to 62 per cent as delay increased over the same period among those with circumscribed breast cancers. The summary of the study by Haagensen and Stout (1942) on page 139 shows a decrease in 5 year survivorship from 54 per cent for those with delay of less than 2 weeks to 22 per cent for those with delay of between 2 and 3 years.

On page 144, in their conclusions on their quotations from the literature, Park and Lees state that the relationship between delay in treatment and curability has not been demonstrated. What more impressive demonstration than the above three sets of figures is required? Further, Taylor and Wallace (1947) are quoted on page 143 as saying, "The cases of short duration show a definitely greater curability rate than those of longer duration," in regard to a total group of patients operated upon, although the figures were not given. This review will attempt to show that the rest of the material in the Park and Lees' article fails to detract from the conclusion indicated by the above data that early treatment is effective in breast cancer.

Park and Lees criticize Geschickter's material on the grounds that the assignment of tumors into the circumscribed and infiltrating types may not have been according to criteria which are independent of duration, and that the relation found between duration and curability within each type may thus be meaningless. However, the range of durations within both the infiltrating and circumscribed types was similar, so that duration itself was apparently not a criterion of distinction. Also, the infiltrating type included both smaller and larger tumor sizes, and there was no indication that the range of tumor sizes in this type was different from the range for the circumscribed type, so that tumor size, which is a function of various variables including duration, was also not a criterion of distinction. Furthermore, it has already been shown that even in a total study group of breast cancer cases of varying degrees of intrinsic malignancy, higher survivorship for shorter durations indicates the effectiveness of early treatment, because *there should be no tendency for an undue proportion of the lower intrinsic malignancy types to be included in the cases of short duration.* When an attempt has been made to divide a total study group into groups with similar intrinsic malignancy, and survivorship is found to decrease with increasing duration within each group, then the entire study group is characterized by the same relationship, regardless of any errors in assigning cases to groups. The finding of that relationship within each group of comparable intrinsic malignancy merely validates the assumption that the relationship is true for the entire study group because it is true for each malignancy group, rather than because the short durations contain an excessive proportion of lower intrinsic malignancies.

Park and Lees believe that Geschickter's survival figures for his patients operated upon for infiltrating cancer are out of line with gen-

eral experience, thus prejudicing the conclusion based on them. They do not illustrate their criticism by presenting any other figures for those operated upon for infiltrating breast cancer. Furthermore, even if Geschickter's figures are not typical because his method of selecting patients makes his total study group unrepresentative of the whole breast cancer population, the comparison between cases of short duration and cases of long duration within his study group should still be meaningful. It is suggested that as long as an entire study group of surgical cases is obtained either at random or by a consistent method of selection, a significantly higher survivorship for the cases of shorter duration indicates the effectiveness of early treatment, since there *is no apparent reason why the cases of short duration should contain an unduly high proportion of the intrinsically lower malignancies found in the total study group.*

Several of the quotations used by Park and Lees seem to contradict the conclusion that early treatment is effective, until they are carefully examined. Thus, the quote from Taylor (1932) on page 137 in which Buchanan is reported as having found a higher incidence of cure among patients operated on 1 to 13 years after onset of symptoms than among those operated on within a year of onset purports to show that delay did not decrease survivorship. But the breakdown of delay into the two categories of under a year and a year or more is entirely inadequate for the purpose. The cases of longer delays in the 1 to 13 year category were obviously of the intrinsically low malignancy type, since these patients could still be alive and in operable condition after such long delays. The fact that their survivorship was fairly good is not at all surprising, and it is seen that the series of Eggers and associates and of Haagensen and Stout showed a similar rise in survivorship for the patients with longest delay before treatment. However, the latter series indicate a decreasing survivorship with increasing duration over the several year period immediately following onset of symptoms. The lack of a finer breakdown of the period of delay vitiates the comparison which had been made by Buchanan.

Park and Lees' quote from Davis (1920) on page 137 reports that, "the average time between the discovery of the 'lump' and the operation of those that died of recurrence is practically the same as of those that have remained free of the disease." It has been amply demonstrated that the cases of very long delays tend to be of low intrinsic malignancy and these patients tend to survive. Therefore, similar average duration figures for the dying and surviving groups indicate that the intervals for the surviving group included a higher proportion of short durations in which delay had been minimized along with the higher proportion of very long durations in which intrinsic malignancy was very low, while the group who died included a higher proportion of middle durations. This would be compatible with a finding of decreasing survivorship with increasing duration over the period up to approximately 2 years after onset of symptoms. Therefore, Davis' data do not detract from the conclusion that early treatment is effective in breast cancer. The same comments apply to the data of Robinson (1948), reported by Park and Lees on page 142.

On page 140, Park and Lees give a quotation from Hawkins (1944), the crux of which is the following statement: "Although significant correlations existed between the duration of the disease and the stage of the disease at first treatment, the duration of the disease was not correlated with survival rates when corrections were made for the stage of the disease. Thus, patients having a history of shorter duration tended to have earlier stages of cancer than did those with long histories; but duration per se contributed little to the determination of prognosis which could not be more directly established by considering only the stage of disease at first treatment."

An examination of the article by Hawkins shows that he did not state the method he used for correcting for stage of the disease when investigating the relationship between duration and survival, and we cannot tell if this correction was appropriate. The result showing lack of correlation between duration and survival after this correction is, therefore, of unknown validity. There is also no apparent reason for such a correction. Since higher

survivorship was associated with lower stage, and lower stage was significantly correlated with short duration, it follows that higher survivorship was associated with shorter duration. This has already been shown to indicate that early treatment is effective. The conclusion is not weakened by the fact that stage was also low when duration was short. It is perfectly plausible that lack of delay should tend to result in diagnosis at an earlier stage, and the fact that it does so certainly does not eliminate the importance of early treatment in the higher survivorship found for cases of shorter duration.

The only quotation used by Park and Lees in their summary of the literature which directly contradicts the conclusion that early treatment is effective is the one from Nathanson and Welch (1936) on page 141. This quotation includes the statement that for the study group in question, "patients with the shortest delay to treatment have the worst prognosis." This is a result which is the direct opposite of those obtained by Eggers and associates, Geschickter, Haagensen and Stout, and Taylor and Wallace, and it causes wonderment as to how such a contradictory result can occur if early treatment is really effective. However, the problem has proved not to be real.

An examination of the Nathanson and Welch article shows that they do not give any of the figures on which this conclusion was based, and that the quotation by Park and Lees represents the original article's complete coverage of the subject. There is no indication as to how much worse the survivorship was for short durations, and the intervals of duration used were not mentioned. Perhaps the breakdown of duration was into categories similar to the ones used by Buchanan, which have been shown to be inadequate. Furthermore, the statement comments only on patients with the shortest delay, and it is possible that survivorship still decreased with increasing duration in the period from the second shortest interval used to 2 or 3 years after onset of symptoms.

However, even if it is assumed that survivorship increased with duration over an adequate set of duration intervals in the Nathanson and Welch study, this may still be compatible with the viewpoint that early treatment is effective. This is due to the fact that the Nathanson and Welch study was made before the other studies which it seems to contradict, being based on data for the years 1923 to 1932, which was well before the current campaign for early treatment had gained momentum. The possible effect of this on the relationship between duration and survival is illustrated in the following numerical example:

Assume for simplicity that there are only two degrees of intrinsic malignancy and that there are only two intervals of duration. Assume that the distribution of the cases by intrinsic malignancy and duration is as follows for year 1, prior to the campaign for early treatment:

Malignancy type	Total cases	Cases with given delay	
		Less than 2 months	2–5 months
A	1050	800	250
B	1050	200	850

Assume that another group of cases with the same proportion of cases in each level of intrinsic malignancy was distributed as follows for year 2, after the campaign for early treatment has begun to have some effect:

Malignancy type	Total cases	Cases with given delay	
		Less than 2 months	2–5 months
A	1050	950	100
B	1050	600	450

The proportionate distribution of cases by malignancy type within each interval of delay for each year is then as follows:

Year	Malignancy type	Percentage distribution of cases with a given delay	
		Less than 2 months per cent	2–5 months per cent
1	A	80	23
	B	20	77
	Total	100	100
2	A	61	18
	B	39	82
	Total	100	100

Assume that the 5 year survivorship by malignancy type and delay was as follows for cases operated on in both year 1 and year 2:

Malignancy type	Delay less than 2 months, per cent			Delay 2–5 months, per cent		
	Total cases	Survived 5 years	Died within 5 years	Total cases	Survived 5 years	Died within 5 years
A	100	30	70	100	15	85
B	100	80	20	100	50	50

By applying the 5 year survival rate for each grade of malignancy to the proportion of the cases that were of that grade in each year, and summing the products, it is found that the total 5 year survival rates by interval of delay and year is as follows:

Year	Delay less than 2 months, per cent			Delay 2–5 months, per cent		
	Total cases	Survived 5 years	Died within 5 years	Total cases	Survived 5 years	Died within 5 years
1	100	40	60	100	42	58
2	100	50	50	100	44	56

It can be seen that in year 1, survivorship increased with delay, but in year 2, survivorship decreased with delay.

It is apparent that *the relationship between survivorship and duration can be reversed as a result of a tendency to decrease delay*. The numbers used in the example are completely hypothetical, and it cannot be said that the example represents the respective situations in the Nathanson and Welch study group or the later study groups from a quantitative standpoint. However, the example demonstrates that the Nathanson and Welch statement does not necessarily contradict the hypothesis that early treatment is effective.

To summarize the review of the literature presented by Park and Lees, this literature provides concrete evidence that early treatment is effective to a very considerable extent in breast cancer cases. The literature fails to provide any evidence to detract from this conclusion.

In part III of their article, Park and Lees present a table relating incidence of axillary metastases at time of radical mastectomy to interval between onset of symptoms and operation in their total study group of radical mastectomy cases. They do several simple linear correlations on the data in this table, and use the table and the regression line to estimate the percentage of cases of detectable axillary metastases at the time of onset of symptoms and over the next 3 year period. As was already pointed out in the discussion regarding Park and Lees' second estimate of maximum curability, the intrinsically higher malignancies tend to come to treatment sooner and the intrinsically lower malignancies tend to come to treatment later, so that the experience for an actual study group of treated cases cannot be used as the basis for a generalization regarding the incidence of axillary metastases after various durations among the entire breast cancer population. This whole population would probably have well under the 60 per cent axillary metastases at time of treatment estimated by Park and Lees if they were all treated as soon as possible, and would certainly have well over the 75 per cent axillary metastases before or at the time of treatment estimated by Park and Lees if no one was treated until he had survived 3 years. The conclusions following from these estimates in part III are, therefore, invalid.

In part IV of their article, Park and Lees analyze the relationship between axillary metastases, survival rate, and survival time. For this purpose, they use a single large and completely examined series of radical mastectomy cases reported in the literature, in which the percentage with axillary metastases, the 5 year survival rate, and the mean survival time of those dying within 20 years of operation are reported for each of the 4 histologic grades of malignancy.

In Figure 4 on page 148, the 5 year survival rate is graphed against one X axis and the average survival time of those dying within 20 years against another X axis. The Y axis in both cases is the percentage of cases of axillary metastases, and the two lines each contain 1 point for each of the 4 histologic grades of malignancy.

Park and Lees assume that the average survival time of those dying within 20 years is a criterion of the intrinsic malignancy, apparently reasoning that those who died were not cured by operation, so that the course of their disease after operation was determined by intrinsic malignancy alone. They observe that the line representing the 5 year survival rate runs parallel in Figure 4 to the line represent-

ing average survival time of those dying within 20 years, and believe that this parallelism is important enough to prove the hypothesis that early treatment is ineffective. They are apparently reasoning that since the 5 year survival rate and the average survival time of those dying within 20 years increased to the same extent when percentage with axillary metastases decreased, the increase in 5 year survivorship was completely accounted for by the decrease in intrinsic malignancy.

The assumption that the average survival time of those dying within 20 years is a good criterion of intrinsic malignancy is questionable. Park and Lees admit that surgery may increase the average survival time of those who die. Furthermore, the data did not separate out deaths from causes unrelated to the original cancer, which would become a big factor in a 20 year follow-up on a group of cancer patients of typical age. There may have been many complete cures of the cancer among those who died within 20 years of operation. The above arguments show that the average survival time of those who die within 20 years is not a good criterion of intrinsic malignancy, and detract from Park and Lees' conclusion to that extent.

However, even if the assumption discussed were good, Park and Lees' interpretation of the parallelism of the lines in Figure 4 seems very arbitrary. The line representing the 5 year survival rate is graphed against an X axis in which per cent is the variable, and the average survival time of those dying within 20 years is graphed against an X axis in which years is the variable. There is no relationship between unit distances on these two axes, and the parallelism of the two lines can be completely destroyed by spreading out the spacing of one of these axes. The observed parallelism, therefore, means nothing.

It has been demonstrated that Park and Lees do not succeed in showing that the markedly higher 5 year survivorship for cases of short delays than for cases of long delays before treatment is due primarily to differences in intrinsic malignancy of the cancers. It is tempting to attribute the whole improvement in survivorship for the cases of short delays to reduced delay itself. However, another factor may be involved to some extent. Each of the studies which found decreasing survivorship with increasing delay probably used a series of patients who had been operated on over a 10 to 20 year period of time. Delay was not reported by year of operation, but it is likely that because of the campaign for early treatment, a greater proportion of patients with short delays were operated on in the more recent years of the study period than was the case for those with longer delays. There have been many improvements in preoperative, operative, and postoperative methods which may have increased survivorship in recent years, and may thus have helped to result in a higher 5 year survivorship for the cases of short duration than for those of long duration. Therefore, we cannot say that the whole quantitative difference in survivorship for these two groups is due to reduced delay itself. To do this, we would have to compare 5 year survivorship for cases of short and long delays in a study group of patients who were operated on over a period that is too short for improvements in technique to result in a significant increase in survivorship. However, if part of the difference in survivorship in the reported series is due to improvements in treatment technique, it follows that treatment can be effective. This means that in a significant proportion of cases, an operation can be performed before metastases have disseminated and that such metastases would have disseminated if no operation had been given. If that is the case, it would appear obvious that the earlier the treatment the more likely the prevention of metastasis and the better the prognosis. Thus, even if an unknown part of the increased survivorship found for cases of short duration is due to improved treatment technique rather than reduced delay itself, it would appear to be the inevitable conclusion that the earlier the treatment the more effective it will be.

It has thus been shown that the literature reviewed by Park and Lees includes four different studies which impressively demonstrate that early treatment is effective in the treatment of breast cancer. Nothing else in the literature they reviewed or in the other arguments used detracts from this conclusion.

An article by Harrington, published since the appearance of the article by Park and Lees, contains data which further indicate that treatment is effective in breast cancer. In Table 2, Harrington gives the 5 year survival rates after radical mastectomy for patients operated on at the Mayo Clinic during successive 5 year periods between 1910 and 1944. *A very definite and consistent increase in the rates was found* in both the group with axillary nodal mestatasis at the time of operation and the group without such metastasis. It is especially interesting that such an increase was found in the group with metastasis. There is no problem of false positive diagnoses of cancer to complicate the interpretation of results in this group. There is also no apparent reason for arguing that the patients in the later years survived better because they represent a lower level of intrinsic malignancy, since the entire group had observable metastases at the time of operation. It appears that the improvement in survivorship in this group must be due to improved and earlier treatment.

The results are also interesting because they suggest that certain significant steps in the course of breast cancer occur at quite a late stage of the disease, and can be prevented by effective treatment without further delay. The very fact that not less than 20 per cent with axillary metastasis survived 5 years after radical mastectomy in each of the 5 year periods indicates that the disease can be cured by radical mastectomy, or at least that generalized metastasis and death can be very significantly delayed, in a sizable proportion of patients who already had axillary metastasis. Apparently there is an appreciable length of time after axillary metastasis in which the generalized spread of the disease can still be prevented and the disease eradicated. It seems very unlikely that a spontaneous halt would have occurred without treatment in these cases, since the disease had already spread spontaneously to the axilla. It is even more unreasonable to argue that the increase in 5 year survivorship for the group with metastasis from 23.4 per cent in 1910 to 1914 to 39.4 per cent in 1940 to 1944 was due to an increase in the number of spontaneous halts that occurred independently of the treatment. This increase indicates that improved treatment, performed with reduced delay, was able to increase survivorship even after axillary metastasis had occurred. This greatly strengthens the conclusion that thorough treatment without delay is effective in treating the entire breast cancer population.

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CONTROL OF INFECTIONS ASSOCIATED WITH OBLITERATIVE ARTERIAL DISEASE

CHESTER W. HOWE, M.D., F.A.C.S., Boston, Massachusetts, and
WILLIAM C. WIGGLESWORTH, M.D., Ipswich, Massachusetts

INFECTIONS are prone to develop in the presence of obliterative arterial disease despite current methods of treatment including the use of antibiotics. This is due in part to the fact that sufficient concentration of drug cannot be carried to the tissues by the partly occluded arterial tree. Once infection is superimposed upon tissues already compromised by vascular insufficiency, it adds to the vicious process by further destruction of cells, increasing the likelihood of thrombosis and in some instances by inducing increased reflex vasospasm. Antibiotics are not effective in the presence of necrotic tissue and its adequate and complete removal is a prime requisite to successful therapy. If the infection is allowed to advance into inaccessible tissue planes proper débridement can be accomplished only by amputation—the fate of many patients with this disease. Certain extremities that succumb to the combined action of vascular insufficiency and infection and in which the latter process is a prominent feature will survive if the infectious process can be controlled. Of 319 patients with obliterative arterial disease and diabetes mellitus operated on by McKittrick and his associates for infection of a lower extremity, careful observation of the arterial supply convinced them that although not normal, it was adequate (8). Edwards states that despite systemic antibiotics, uncontrolled spread of infection with consequent added susceptibility to thrombosis was the initiating factor in the decision to amputate extremities of many of his patients. McKittrick and Root (10) and later Williams and O'Kane have evolved classifications based on clinical observations which help to demonstrate whether infection or arterial insufficiency is the predominant factor in each lesion. Otherwise, the literature is apparently lacking in appreciation of the two distinct pathological entities which may be present in these ulcerations.

From the Surgical Service and the Smithwick Foundation of the Massachusetts Memorial Hospitals and the Department of Surgery of Boston University School of Medicine, Boston, Massachusetts.

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This paper presents observations on 21 patients in whom a special attempt was made to control the infectious component of the disease. One of the foremost problems in this respect was to get the proper antibiotic to the site of infection in the correct concentration.

SYSTEMIC ANTIBACTERIAL TREATMENT IN OBLITERATIVE ARTERIAL DISEASE

All except 1 of the infections in this group of patients had persisted and advanced despite systemic antibiotic treatment before study.

Inability to attain satisfactory antibacterial effect at the site of the infection has led to attempts to overcome this problem by the direct injection of antibacterial substances into the arterial supply of the extremity. This method has not appealed to us because of the lack of convincing evidence of its efficacy, and because of the danger of dislodging atheromatous plaques or inducing further reflex vasospasm by multiple needle punctures in an already impaired artery.

We have for the most part continued to use systemically administered antibiotics in our cases because, although such therapy does not always control the local infection, it may be of considerable value in limiting the extent of spread and preventing septicemia and embolic complications at a distal site. The fact remains that these infections frequently persist and spread despite the best antibiotic regimes and ancillary supportive measures.

TOPICAL ANTIBACTERIAL TREATMENT IN OBLITERATIVE ARTERIAL DISEASE

The general disfavor in which topical antibiotic therapy is regarded has been based

largely upon the failure of the sulfonamides to control infections when applied locally. McKittrick (9) was unimpressed with the effects of local penicillin in diabetic patients but stated that it may have been due to inexperience in its proper use. There are numerous explanations for these failures. Among them are the ineffectiveness of antibiotics in the presence of necrotic tissue, inhibiting substances in tissue exudates, difficulty in maintaining adequate constant contact between the drug and the site of the infection, the use of an antibiotic to which the presenting bacterial flora is resistant, failure to develop techniques which prevent recontamination with new resistant organisms when using wet dressings, and the application of certain agents in concentrations which in themselves are toxic to tissues. Further objections are, the possibility of exceeding the optimal concentration for a given drug when dealing with the so called "zonal" organisms described by Eagle, and the supposition that topically applied antibiotics will not penetrate sufficiently to effect bacteria harbored deeply in lymphatics or granulation tissue. In addition, the authors have frequently observed instances in which antibiotics have been applied topically to lesions in which a true infectious component was lacking and in which the vascular component was the predominant factor. The failure of the lesion to heal was then erroneously attributed to lack of efficiency of the antibiotic.

It is a well known fact that simple, meticulous wet dressings of saline or Dakin's type solutions are effective against many infections, especially those of a saprophytic noninvasive nature. This discussion does not concern itself with lesions of this type. The authors frequently use saline or Dakin's solutions with good results. We are concerned rather with the invasive ulcerative or gangrenous type of lesion which persists or advances despite such treatment. Eight of the cases reported here had received wet saline or boric dressings for varying lengths of time before treatment by us.

The aforementioned objection directed at the possibility of exceeding the optimal concentration for zonal organisms when using topical therapy would seem invalid because it is possible to adjust accurately the concentration of topically applied agents to the desired level whereas no satisfactory means have yet been devised to control or determine tissue levels when using systemic therapy clinically. Furthermore, the authors (4, 6) and Schaffer and associates have shown that certain antibacterial agents (e.g., urethane, penicillin, bacitracin), when applied topically to skin or exposed tissue, are capable of penetrating and being absorbed to such an extent as to give detectable blood levels.

Because of these facts and on the basis of our experiences we have formulated certain requisites which we consider to be necessary for the successful use of topical antibacterial therapy in general. They are (1) the absence of necrotic tissue, (2) susceptibility of organisms to the antibacterial agent, (3) adequate constant contact between the site of infection and the drug, (4) prevention of recontamination with resistant organisms, and (5) the use of agents which in themselves are well tolerated by the tissue being treated and not inhibited in the wound.

Situations in which it seems logical to apply topical therapy may be divided into two main categories. The first of these includes areas of the body in which it is not possible to attain blood or tissue levels of antibiotic sufficient to exert a bacteriostatic or bactericidal effect. In this category it is important to remember that antibiotics do not diffuse readily into bone or cartilage and that diffusion into cerebrospinal, synovial, and pleural fluids is slow and in much lower concentration than in the blood. In the presence of a scar tissue barrier or vascular insufficiency, adequate tissue levels will not be obtained. In the second category are included infections in any area, caused by bacteria which are not susceptible to tissue concentrations of antibiotic that can possibly be obtained by systemic administration. It is not the purpose of this paper to discuss the ranges of concentration of the antibiotics to which the various bacteria are susceptible or the concentrations of the various agents which may be applied to tissues without causing cell damage.

In view of the foregoing, it seemed to us that infections associated with occlusive arterial disease would be a logical field in which to

study the efficacy of combined topical and systemic antibacterial therapy.

METHOD OF STUDY AND CLASSIFICATION OF CASES

The 21 cases reported here were selected in a sense, because they represent mostly the more severe types of disease referred to us because of our special interest in surgical infections. There were 13 females and 8 males whose ages were evenly distributed throughout the fifth to the eighth decades of life except for 2 young males. One, aged 36 years, had Werner's syndrome. The other, aged 25, had chronic sepsis and vascular thrombosis in a traumatic amputation stump. The primary diagnosis in all instances, except for the traumatic amputation, was arteriosclerosis of the lower extremities with superimposed infection. Severe ulcerations were present in 20 patients and gangrene, either alone or associated with ulceration, was present in 7. A marked cellulitis surrounded the lesion in 13 instances. These lesions were further complicated by the presence of diabetes mellitus in 7 patients, underlying osteomyelitis in 4, and nitrogen retention in 1.

The bacterial flora consisted mainly of Staphylococcus aureus, streptococci of various types, organisms of the coli-aerogenes and proteus groups and Pseudomonas pyocyanea. Occasional strains of diphtheroids, Bacillus mucosus, Monilia albicans, and Bacillus subtilis were found.

A simple three group classification has been used depending upon the relative predominance of the infectious or vascular component. The extent and severity of the infectious process was determined by clinical observation. The degree of vascular pathology was judged not only by an evaluation of the peripheral pulses and flushing and venous filling time but also by skin temperature studies and plethysmography in most instances and tissue biopsy whenever it could be performed without hazard to the patient. The classification is:

Group I. Lesions in which vascular damage is minimal and infection is the predominant feature.

Group II. Lesions in which both infection and vascular insufficiency are present and threaten the loss of a limb but in which the vascular damage alone is not a great hazard.

Group III. Vascular insufficiency is the predominant feature: (a) dry gangrene with saprophytes and no invasive infection; (b) extensive superimposed infection of bone, tissue planes, or tendon sheaths.

Biopsies of the lesions from group I patients show minimal intimal thickening. There is a moderate inflammatory response evidenced by polymorphonuclear cells and lymphocytes in the lumens of the blood vessels and in the surrounding tissues. In group II cases the arteries have markedly thickened walls due to increased fibrocollagenous material. There is smooth muscle degeneration, intimal thickening, and some hyperplasia of the endothelial lining. In general there is but slight chronic inflammatory response manifested by scattered lymphocytes in the tissues. Group III biopsies show stenotic arterial walls with thickening of both intima and media. There is perivascular and perineural fibrosis and some intramural vascularization. Very little inflammatory response is seen.

Aerobic and anaerobic cultures were taken routinely several times before and after treatment. All cultures were planted on blood agar and eosin methylene blue plates and inoculated into 6.0 milliliters of beef heart infusion broth containing sheeps' blood and 5.0 milligrams per cent of para-aminobenzoic acid. Tubes of cooked meat media and infusion broth sealed with petroleum jelly and paraffin were used for anaerobic cultures.

Clinical results are expressed as the time required to control the infectious as distinct from the vascular factor. The latter is represented by measuring the time required to achieve a definitive end result either by complete healing of the lesion or healing of the amputation stump.

TREATMENT

All except 1 of the patients were receiving either penicillin, streptomycin, gantrisin, or one of the other broad spectrum antibiotics systemically at the time they were first seen. This treatment was continued for reasons explained in all except 3 patients. Antibacterial agents for both systemic and topical adminis-

tration were chosen on the basis of the bacterial flora aided by routine sensitivity tests by the filter paper disc technique. In special instances, additional sensitivity studies were carried out by using the serial dilution method of Rammelkamp.[1] Antibiotics were given systemically either alone or in combination as indicated. Penicillin was used most frequently (18 patients) with streptomycin next (7 patients). Chloramphenicol was used 3 times and terramycin and aureomycin once each.

A solution of 5 per cent sulfamylon containing 200 units of streptomycin per milliliter as advocated by Howes (5), was found to be the combination of choice for topical treatment in 12 instances. Glycerite of hydrogen peroxide with 4 per cent urea was used in 3 patients, a 10 per cent aqueous solution of urethane in 3, penicillin, 1,000 units per milliliter in saline in 2, and bacitracin, 500 units per milliliter in 2. Streptokinase and streptodornase were used as an aid to débridement in 1 necrotic ulcer containing fibrin and pus. A surgical soap containing G-11 was used in 3 instances for its antiseptic value.

All of the usual supportive methods such as bed rest, Buerger's exercises, and careful aseptic measures were carried out as indicated in conjunction with the antibacterial therapy.

After studies were completed, topical treatment with an appropriate agent or combination of agents was instituted. The following technique was devised in an attempt to satisfy the requisites for successful topical therapy as outlined previously.

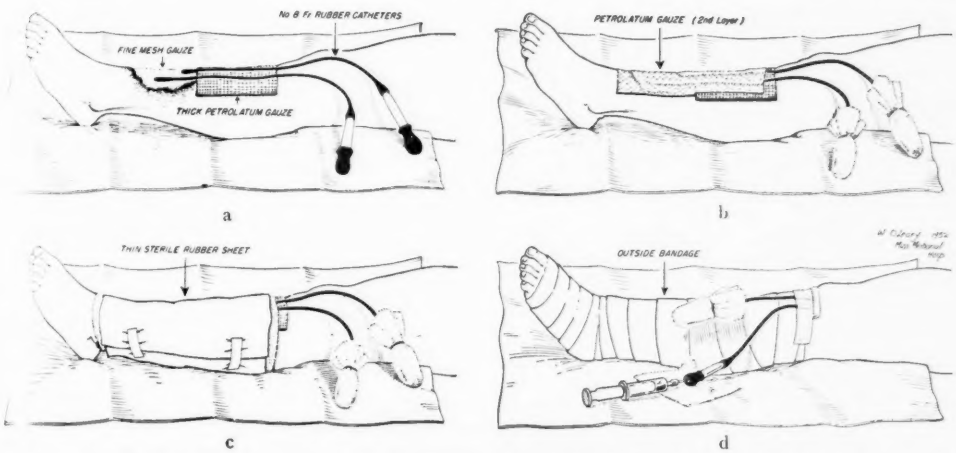
METHOD OF DRESSING

Surgical masks and sterile gloves and drapes were used during all dressings. In most instances, adequate débridement could be carried out on the ward but very painful lesions or those with an excessive amount of necrotic tissue were débrided in the operating room under anesthesia.[2] A layer of gauze was then placed over the clean débrided lesion, trimmed to fit its geographical pattern and so placed as to act as a wick to carry the medication into all crevices (Fig. 1a). Bulky gauze dressings soak up the antibiotic solution and keep it out of the wound. Thin, accurately placed gauze is easily saturated with small amounts of antibiotic solution which is fed to it through one or more No. 8 or 10 French rubber catheters. Since slight pressure from the outside bandage on a rubber catheter may groove the skin and start a new ulceration in these extremities with a poor vascular supply, a generous protective thickness of petrolatum gauze is placed beneath each catheter in the area where it contacts the skin (Fig. 1a). An additional sheet of well lubricated petrolatum gauze is then placed over the whole area (Fig. 1b). This serves not only to hold the catheters in place while the outside dressing is being applied, but also to help make the dressing waterproof and prevent evaporation of the solution. Another more bulky layer of surgical gauze is then placed outside of the petrolatum strips and covered with sterile rubber sheeting or plastic material (Fig. 1c). The purpose of this is to make the dressings as occlusive as possible. Colebrook and Hood have shown that organisms (especially motile ones) can penetrate rapidly a wet dressing and contaminate the wound. This is prone to occur where the wet dressing comes in contact with the bed clothes, attendants' hands, or other contaminated objects. The catheters emerge through a final outside layer of loosely applied bandage which serves to hold the rubber sheet in place. Sterile medicine droppers are inserted into the open ends of the catheters (Fig. 1d). Solutions are injected with a needle and syringe by puncturing the sterilized rubber bulb of the medicine dropper which is kept covered with sterile gauze between injections. Insertion of 2 to 4 milliliters of solution into each catheter every 4 to 6 hours, depending on the size of the lesion, will keep the wound wet and in constant contact with a fresh supply of solution. Since such small amounts are administered, much of the solution will remain in the bulb or in the catheter unless it is blown through with air following each injection.

Dressings are left in place 4 to 6 days before removal. It has been our observation that the

[1]The pitfalls of choosing antibiotics by the use of bacterial sensitivity tests are well known and have been reviewed by Jackson and Finland. The authors believe that such tests are of definite value providing one is aware of the errors that can be encountered by using the various methods and that the final selection of an agent is tempered by experienced clinical judgment.

[2]Extreme caution is advocated in attempting surgery on limbs with severe arterial occlusion unless the collateral circulation is adequate.



g. 1. Technique of dressing. a, A layer of fine mesh is placed over the lesion, thick enough to act as a voir for the antibacterial solution but not so bulky as ld the medication away from the lesion by absorption. eters for the instillation of medication are protected grooving the skin and starting new ulcerations by a underlying sheet of petrolatum gauze strips. Sterile icine droppers are inserted into the open ends of the eters to facilitate aseptic injection of medication by turing the rubber bulb with a hollow needle. They are ected with sterile gauze between injections. b, An addi- l generous layer of petrolatum gauze is placed over the catheters to hold them in place and help make the dressing waterproof. c, A layer of rubber or plastic sheeting is incorporated into the dressing to make it as waterproof as possible and prevent recontamination of the wound by permeating of organisms through the dressing. d, Catheters are led through an outside layer of loosely applied bandage. Dressings are left in place 4 to 6 days. Injections of 3 to 5 milliliters of antibacterial solution into each catheter every 4 hours will keep the lesions constantly moist with a fresh supply of the chosen drug. The waterproof nature of the dressing prevents evaporation and allows treatment with small inexpensive amounts of antibiotics.

ximal effect of topical therapy is usually ac- plished within this period and that noth- is to be gained by more prolonged therapy. If the infection has not been controlled at the end of this time, re-evaluation by repeat cultures and sensitivity testing may indicate that the flora has changed, and a resistant organism has become predominant. If further necrosis has developed, another débridement and a change of antibiotic according to the new findings may be indicated.

Although some wrinkling of the surrounding normal skin may be present upon removal of the dressing, maceration of the tissues has not been encountered while using these small injections of antibiotic solution for periods of 4 to 6 days. No instances of sensitivity from topical application of drugs were seen in this series of cases. Occasionally, when excess amounts of solution containing the drug sulfamylon were used, deposits of small crystals collected about the lower end of the dressing causing slight skin irritation. Otherwise, there were no untoward effects. We would hesitate to use irritating solutions such as Dakin's or hypochlorite beneath such an occlusive dressing.

We believe that the meticulous care in preparing the wound and dressing is fully as important in obtaining a favorable result as is the antibacterial effect of the medication. Although time consuming, this type of dressing is actually labor saving in the end because it obviates the necessity of further changes for the next 4 to 6 days. It reduces the hazard of recontamination from repeated dressings and allows for the efficient use of small amounts of antibiotic, thereby lowering the expense to the patient.

After the infection has been controlled, healing may progress to completion or may become arrested after partial epithelization. Such ulceration as remains after the infection is obliterated is due solely to the vascular component of the disease. Decision as to further surgical treatment such as sympathectomy or

Fig. 2. Example of group I lesion. Ulceration of 6 months' duration on the leg of a 77 year old Chinese male with minimal arteriosclerosis. Glycerite of hydrogen peroxide with urea was used for chemical débridement followed by bacitracin ointment. Healing was complete on the thirteenth day after beginning treatment.

amputation then depends upon a re-evaluation of the vascular status to determine the extent of healing, the presence or absence of a significant vasospastic element, the patency of the main blood vessels, and state of the collateral circulation.

RESULTS OF TREATMENT

Group I. There were 4 patients in this category. None were diabetics. Cultures in 2 cases showed a profuse mixed gram positive and gram negative flora, whereas the other 2 were pure gram positive infections. All patients had received systemic antibacterial therapy which failed to control the infection. Although 3 of the patients had previous short periods of wet saline dressings, it is probable that success would have resulted if this form of therapy had been continued for a longer time. All cases responded promptly when topical therapy was added.

Pretreatment cultures from this group yielded streptococci from 3 of the lesions, members of the coli-aerogenes group from 3, Staphylococcus aureus from 2, diphtheroids from 2, and Bacillus mucosus from 1. In the posttreatment cultures, Staphylococcus aureus, Escherichia coli, and Streptococcus pyogenes each appeared once, all the other strains having disappeared from the flora. Moreover, these cultures yielded only a few colonies on agar plates whereas before treatment growth was profuse. The total number of strains of bacteria was thus reduced from 10 to 3 by treatment. The time required to control the infections ranged from 2 to 13 days with an average of 5.5 days for the group. Skin grafts were successfully carried out on 2 patients following control of the infection. There were no sympathectomies or amputations. The time required for complete healing ranged from 13 to 35 days with an average of 25.5 days for the group. Figure 2 is an illustrative example of the type of lesion in this category.

Group II. There were 9 patients in this group of which 4 were diabetics. All lesions contained mixed gram positive and gram negative organisms except for 1 which was due to a pure culture of Pseudomonas[1] and another which was a pure gram positive infection. Three patients had previous wet saline dressings.

Before treatment, Staphylococcus aureus was recovered from 7 of the lesions, coli-aerogenes organisms from 4, streptococci and Pseudomonas pyocyanea each from 3, Proteus from 2, and miscellaneous other organisms once each from 5 lesions. The total number of bacterial strains was reduced from 24 to 11 by treatment. Staphylococcus aureus disappeared from the flora 4 times, coli-aerogenes organisms 3 times, streptococci twice, Proteus once, and miscellaneous other organisms 3 times. Pseudomonas pyocyanea persisted in all 3 lesions in which it was originally present, but as with all persistent strains, posttreatment cultures showed only an occasional colony on blood agar plate culture.

The clinical response in this group was most satisfactory and it is believed that the greatest benefit can be derived from intensive antibacterial therapy in this type of case. The time required to control the infectious component of the disease ranged from 4 to 18 days with an average of 8.1 days for the group.

Following control of the infection it was necessary to perform lumbar sympathectomy on 4 patients, a low thigh amputation on 1 patient, and skin grafts on 3. One patient was treated for postoperative sepsis in an amputation stump. The time required to obtain a

[1]Previously reported (4).

definitive end result following control of the infection ranged from 17 to 103 days with an average of 47 days for the group. It is apparent, therefore, that control of the infectious component required a relatively short time in comparison to control of the vascular component as manifested by complete healing.

Seven of the lesions in group II patients were in the soft tissues of the leg above the ankle and excessive pain was a prominent feature. It is noteworthy that when the infection was controlled the pain disappeared in most instances.

The following case history illustrates the difference between the infectious and vascular components of the disease and demonstrates the superiority of specific topical antibacterial therapy over wet saline dressings. The patient presented extensive bilateral ulcerative lesions of both lower extremities. The right leg which was most severely involved, was treated with a solution of 5 per cent sulfamylon containing 200 units of streptomycin per milliliter, whereas the left leg was treated in identical fashion using saline.

S. C., M.M.H. 347,876, a 63 year old American Slow, entered the Massachusetts Memorial Hospitals on November 20, 1950 with multiple painful infected ulcers on both lower legs of 8 months' duration. Ulceration was first noted in April, 1950 following slight trauma in the pretibial region on the right. Shortly thereafter the right leg became ulcerated and the lesions advanced progressively despite treatment with various ointments. There was no history of claudication or diabetes mellitus.

Physical examination revealed a thin, poorly developed woman in obvious pain. The heart showed frequent extrasystoles. The pulse was 90, the respirations were 20, and the blood pressure was 160/70. The temperature varied from 99 to 101.3 degrees F. on the day of admission.

The right leg was the site of large confluent skin ulcerations extending from the midleg to the ankle. The lesions were not full thickness except in 2 areas anteriorly and posteriorly, each approximately 2 by 3 centimeters. The left leg had 2 less severe ulcers, approximately 5 by 8 centimeters and 10 by 12 centimeters over the anterior and posterior surfaces respectively, 3 inches above the ankle. The femoral arterial pulsations were diminished. The popliteal pulsation was barely palpable on the left but absent on the right. No arterial pulsations were discernible below the popliteals.

The hemoglobin was 12.4 grams per 100 cubic centimeters and the hematocrit was 38 per cent. The white cell count was 16,000 with 75 per cent polymorphonuclear cells. The urine was normal except for a trace of albumin. The fasting blood sugar was 85 milligrams per 100 cubic centimeters.

Roentgenograms of the legs showed only demineralization of some of the bones of the ankle joints. Skin temperature studies after 1 hour in the cool room at 68 degrees F. showed the temperature at the tip of the right great toe to be 71 degrees F. and of the left great toe to be 73 degrees F. Readings after 1 hour in the warm room at 83 degrees F. showed the temperature of both great toes to be 88 degrees F.

The patient was given continuous wet saline dressings with changes every 6 hours and procaine penicillin, 300,000 units daily for a period of 5 days. She complained of persistent pain despite ½ grain of codeine sulfate and 10 grains of aspirin every 4 hours. No improvement was noted on this treatment and because of the extreme pain caused by changes of the saline dressings, they were abandoned in favor of petrolatum strips. No further systemic antibiotics were given.

Bacteriological cultures of the lesions of the right leg at this time revealed the presence of Pseudomonas pyocyanea (Bacillus pyocyanea), Aerobacter aerogenes, nonhemolytic streptococcus (enterococcus type), nonhemolytic Staphylococcus aureus and diphtheroids. Cultures of the left leg showed Pseudomonas pyocyanea, Aerobacter aerogenes, and nonhemolytic Staphylococcus aureus.

Bacterial susceptibility tests were carried out for a number of antibacterial agents and data indicated that a combination of sulfamylon and streptomycin, although not completely inhibitory, was the selection of choice.

On December 6, after 10 milligrams of morphine sulfate and 75 milligrams of demerol were administered, the legs were débrided of all small bits of necrotic tissue until both were clean. They were then wrapped in occlusive, waterproof dressings with sterile gauze wicks over the lesions (Fig. 1). Treatment for the right leg consisted in injecting 5 milliliters of 5 per cent sulfamylon containing 200 units of streptomycin per milliliter into each of 3 catheters every 4 hours. Five milliliters of normal saline solution were injected into each of the 3 catheters of the left leg at the same time intervals.

Treatment was continued for 6 days and dressings were removed on December 11. Removal of the left leg bandage was extremely painful. The lesion was foul and odorous and there was an advancing edge of skin necrosis around each ulcer (Fig. 3a) not previously present. There was purulent material and green pigment on the gauze. Removal of the dressing from the right leg was painless and the lesion was clean. Epithelization of the ulcers was complete except for one area 1.5 centimeters in diameter anteriorly (Fig. 3b) and a similar one posteriorly. Cultures of this area showed only occasional colonies of Pseudomonas pyocyanea. Cultures of the saline treated left leg yielded a profuse growth of all constituents of the original flora plus Escherichia coli and Monilia albicans. Streptomycin-sulfamylon

a b

Fig. 3. a, Ulcerative lesions after 6 days of wet saline dressings on the left leg of a 63 year old widow with arteriosclerosis. Infection progressed during treatment. There was necrotic skin not previously present. Removal of the dressing was extremely painful and the lesion was foul and purulent. Green pigment and pus were present on the gauze. This is an example of a group II lesion. b, Lesions on the right leg of the same patient, after 6 days of treatment with 5 per cent sulfamylon solution containing 200 units of streptomycin per milliliter. The area of the original ulceration can be seen from the extent of the new epithelization which has progressed during the treatment period. This leg originally had a larger lesion and contained more organisms than the left leg. The dressing was clean and its removal painless. Bacteriologic findings are described in the text.

treatment was started immediately on the left leg following débridement of the necrotic skin.

Despite the fact that all evidence of infection had disappeared from the right leg the few remaining unepithelized areas refused to show evidence of further healing. Accordingly, on December 26, a right lumbar sympathectomy was done. Following this the remaining small lesions, which were kept clean with intermittent wet saline dressings, gradually began to epithelize. The left leg lagged behind the right in its healing progress. A left lumbar sympathectomy was done on February 16, 1951. At the time of her discharge on May 8, 1951 both legs were healed and painless.

All strains of bacteria were obliterated from the right leg (streptomycin-sulfamylon treated side) except for a few colonies of Pseudomonas pyocyanea. On the other hand, the saline treated side which originally cultured a less profuse flora, yielded posttreatment cultures containing not only its original bacterial constituents but 2 new organisms as well. These bacteriologic data correlate well with the clinical results which are illustrated in Figure 3. The right leg (Fig. 3b), which had originally exhibited the most severe involvement, had almost completely epithelized. The dressings were clean and their removal was painless. The infectious process on the saline treated left leg, however, had spread (Fig. 3a). There was a margin of advancing necrosis around the lesions not originally present. Removal of the dressing was extremely painful and green pyocyaneous pigment and purulent material were present on the dressing.

The infectious component of the disease is represented by the amount of healing which occurred during the 6 day period of specific topical therapy. Following this, further epithelization did not occur until sympathectomy was performed whereupon healing gradually progressed to completion over a period of 69 days.

This patient was originally referred by her physician for the purpose of amputation because of the persistent painful lesions. For this reason and because of the infection, sympathectomy was not done immediately upon admission. In view of the skin temperature studies following control of the infection, however, it seemed reasonable to carry out this procedure.

Group III. Three of the 8 patients in this group were diabetics. Three patients were first presented to us after amputation for treatment of a septic stump so that we had no opportunity to treat the original infection. In these 3 cases, appropriate systemic and topi-

cal therapy served to control the infection in an average of 3 days following which stump healing, requiring surgical revision in 2 instances, was complete in an average of 13 days from the beginning of treatment.

One patient was not suitable for topical therapy, the sepsis having involved tissue planes in such a fashion as to make it anatomically impossible to conform to our requisites for topical therapy.

The remaining 4 patients were treated both systemically and locally. The posttreatment cultures were lost on 1 of these. Bacteriological data were available, therefore, on 3 patients upon whom treatment was carried out for the primary infection. In these, Staphylococcus aureus and streptococci were each cultured from the 3 lesions, and each disappeared from the flora after treatment in 2 instances. Four organisms of the coli-aerogenes group appeared in the culture and were obliterated after therapy in 2 instances. Treatment, therefore, reduced the number of bacterial strains from 10 to 4 in this group.

The time required to control the infectious process in the 4 patients receiving primary systemic and topical therapy averaged 4.7 days. The vascular damage was so extensive in these patients that despite clinical control of the infection, amputation was advised for all 4 of them.

In the group as a whole there were 4 thigh amputations, 1 transmetatarsal amputation, and a removal of the great toe. The other 2 patients upon whom amputation was advised refused and were discharged against advice. The time required from the beginning of treatment to obtain a definitive end result, as manifested by complete stump healing, ranged from 10 to 40 days with an average of 19.6 days.

Antibiotics appear to be of value in controlling the infections in this group, especially when the requisites for successful topical therapy can be satisfied. Despite clinical control of the infection, however, amputation was indicated in all instances. It is probable that preliminary chemotherapy is of considerable protective value in preventing the spread of infection, embolic phenomena, septic amputation stumps, and in some instances even allowing a more conservative amputation. It is obvious, however, that it cannot be expected to influence definitively the healing of the primary lesion or prevent the necessity for amputation when the vascular factor is the predominant one.

Fig. 4. Gangrenous lesion of the foot due to severe obliterative arteriosclerosis illustrative of the group III type of case described in the text. Vascular insufficiency was the predominant feature, and there was little evidence of infection.

Figure 4 illustrates the type of lesion seen in group III (a) in which there is little infection but considerable tissue necrosis.

DISCUSSION

The data reported here illustrate the well known fact that sterilization of a wound is not necessary for healing or for closure. It is necessary, however, to control the spreading infection and to convert the wound into a clean one containing pathogens rather than invasive organisms. In all instances the control of the infection clinically has been associated with a reduction in the flora not only as to the number of strains present but also as to the number of bacteria in the persistent strains. Our data indicate that antibacterial therapy is of distinct value in accomplishing this objective. Although nonspecific wet therapy is quite adequate in the usual case, it frequently fails to control severe infections associated with obliterative arterial disease. Regardless of the type of treatment, the removal of necrotic tissue is of prime importance, for it is

the pablum upon which bacteria thrive and is not penetrated by antibacterial agents. There can be no doubt that specific topical therapy is a useful measure in the control of invasive, progressively advancing infections in certain instances. One case in this series is an illustrative example and has been reported in detail elsewhere (4). Undermining ulcerative lesions such as Meleney's burrowing ulcer are notoriously resistant to wet saline therapy but respond to specific topical treatment. The authors have repeatedly observed infections not associated with peripheral vascular disease which were brought promptly under control with the aid of specific topical therapy. When saline was used to replace the antibiotic these wounds again became purulent or the infection resumed its invasive character only to come promptly under control again upon reverting back to the original antibacterial agent. Such evidence has convinced us that properly applied local treatment has definite value when indicated. The case history reported in this paper gives further evidence in support of this contention. The result of treatment of the right leg with streptomycin-sulfamylon was far superior both clinically and bacteriologically to the result of treating the left leg with saline under identical conditions. Such therapy helps to maintain the delicate balance in favor of the compromised limb in severe infections when every advantage counts.

As a result of these studies we have a clearer orientation as to our objectives in the treatment of infections associated with vascular disease. We have attempted to define our objectives and interpret our results in relation to the extent of the lesion, such as is common practice in other surgical diseases, as for example, cancer and hypertension. In group I cases, we attempt a cure with meticulous surgical toilet and antibiotic therapy. In group II cases, we are endeavoring to use the same principles to control the infectious component and so obviate the necessity of an amputation which might be required if both infectious and vascular components of the disease remained in operation. In group III cases, even though the infection can be controlled, nothing short of radical surgery can accomplish good results and function must be sacrificed if necessary.

The cessation of pain with the control of infection has been a dramatic feature in a few cases. It is conceivable that this might reduce vascular spasm and thus favorably effect control of the vascular factor.

It would be a mistake to attribute the beneficial results entirely to topical therapy. Removal of necrotic tissue, meticulous preparation of the wound and dressings, and systemically administered antibiotics have all played a prominent part. In most instances, however, the lesions persisted and advanced until proper specific topical treatment was added to the therapeutic regime.

SUMMARY AND CONCLUSIONS

1. In infections (group I) which persist and advance despite adequate care and systemic antibiotic therapy and in which vascular insufficiency is minimal, the addition of properly applied topical therapy to the usual supportive measures and systemic antibiotics can control the infectious component and result in healing. The average time required for clinical control of the infection by the method outlined in a group of 4 cases was 5.5 days.

2. When the infectious and vascular components of obliterative arterial disease are relatively equal (group II) a combination of good surgical care, topical antibacterial therapy, and systemically administered antibiotics can control the infectious component of the disease. The average time required for control of the infection in a group of 9 cases was 8.1 days. Following control of the infection, the necessity for sympathectomy or amputation will depend upon an evaluation of the degree of underlying vascular disease.

3. Chemotherapy is of no value in the control of the local disease process in advanced infections of the feet when the vascular component is predominant (group III) and the requisites for successful topical therapy cannot be fulfilled. When the requisites can be satisfied the infectious component may be controlled but this cannot be expected to influence definitively the ultimate healing of the lesion or prevent the necessity for amputation in this group of cases. Antibiotics may be of considerable value in preventing further spread of infection or complications.

4. Control of the infectious component of the disease, when possible, requires a relatively short time in contrast to control of the vascular component.

5. In a case of severe obliterative arterial disease with superimposed infection, the effect of specific topical therapy was demonstrated to be clinically and bacteriologically superior to saline dressings.

6. Objectives in the treatment of infections associated with vascular insufficiency are defined in relation to the severity of the disease process.

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THE EFFECT OF LEG TRACTION ON RUPTURED INTERVERTEBRAL DISCS

SANFORD F. ROTHENBERG, M.D., HOWARD A. MENDELSOHN, M.D., and TRACY J. PUTNAM, M.D., Los Angeles, California

THE criteria of diagnosis and the technique of surgical treatment of rupture or herniation of lumbar intervertebral discs appear to be well standardized, but the same cannot be said of the conservative treatment. Obviously, nonoperative treatment is frequently successful and the use of leg traction is often recommended as a part of the conservative regimen. Our purpose is to study the mechanical effect of leg traction on the vertebral joints adjacent to a ruptured intervertebral disc.

The reasons given for the use of leg traction are seldom clearly defined, but those who have recommended its application in patients with ruptured lumbar intervertebral discs have stated or implied that it tends to bring about distraction of the intervertebral joints and thus reduces the herniation. The opinion has been expressed that skin traction applied to one or both legs causes relaxation of the spasm of the muscles of the back so that the herniated disc can resume its normal position. A search of the pertinent medical literature does not reveal factual evidence to support these contentions. Tanz has stated that, in 30 per cent of subjects over 45 years of age, no motion of the lumbosacral joints can be demonstrated roentgenographically, and that the range of motion at the fourth and fifth lumbar intervertebral joints decreases progressively with increasing age.

We have attempted to determine by direct measurement the mechanical effect of leg traction upon a herniated lumbar disc or upon the adjacent vertebral joints.

METHOD OF STUDY

In order to obtain precise evidence upon this point, we carried out observations at the time of operation on 5 patients suffering from rupture of a lumbar intervertebral disc. The ages of these patients ranged from 21 to 57 years. In all of these cases, the history and examination were typical and a defect was found by myelography. Preparations were made beforehand so that accurate measurements and records could be made, when the disc and surrounding structures were exposed, both before and after the application of traction. The herniations themselves were carefully watched as the weights were applied and removed, and, in addition, careful measurements were taken between fixed points in the bodies (4 cases) or pedicles (1 case) of the adjacent vertebrae. These were made as follows: A hole about 1 millimeter in diameter was drilled into each vertebra, and these were used as points of reference, the distance between them being carefully measured with a pair of dividers (Fig. 1) before, during, and after the application of traction.

The operations were all carried out with the patient in the prone position, and under sodium pentobarbital anesthesia to the point of complete relaxation. Before the weight was applied, the table was flattened and the patient's head was lowered to counterbalance the traction which was applied along the body axis with appropriate countertraction. Traction was begun with 10 pounds on the homolateral leg, then 25 pounds, and then 25 pounds on the contralateral leg in addition, while measurements between the drill holes were taken each time as well as when the weights were removed.

In no single instance was there an observable change in the appearance of the ruptured disc or an appreciable difference in the caliper measurements between the drill holes with and without traction.

Observations of another type were made in the case of a patient 21 years of age, who had

From the Departments of Orthopedic Surgery and of Neurological Surgery, Cedars of Lebanon Hospital, Los Angeles, California.

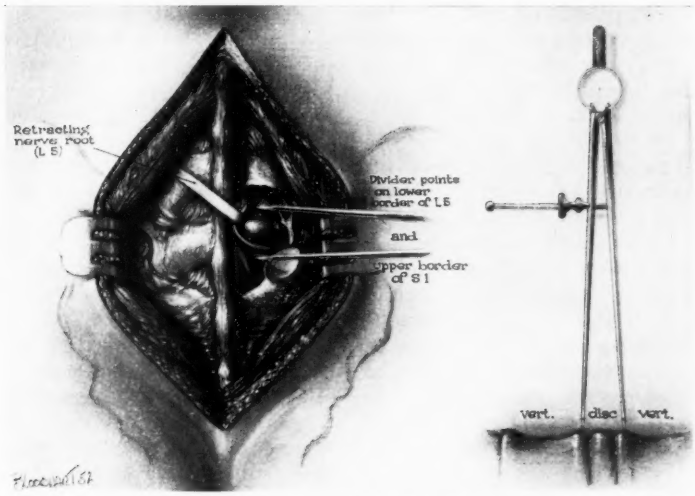

Fig. 1. Drawing of operative exposure of herniated intervertebral disc at the fifth lumbar interspace. A hemilaminectomy permits placement of the divider into the vertebral bodies above and below the herniation. Root is retracted to permit visualization of the herniation and the vertebral bodies. At the right of the drawing can be seen the divider and its placement over the vertebral bodies for measurement before and after leg traction.

een in traction for 3 days with a weight of o pounds applied to both legs which was as nuch as he could tolerate. After local anesthesia with procaine, lumbar puncture needles vere inserted into the bodies of the fourth and ifth lumbar vertebrae and into the neural rch of the first sacral vertebra. The patient was then placed in a supine position on a mattress designed for continuous spinal anesthesia, which allowed the needles to protrude from his back through the opening in the mattress. Lateral and anteroposterior roentgenograms were taken in this same position before and after 5 and 20 minutes respectively

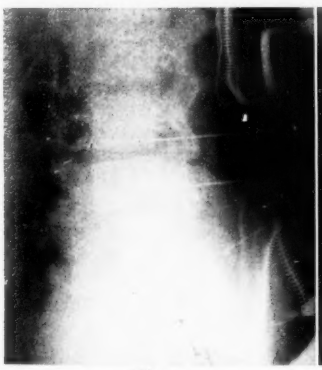

Fig. 2.

Fig. 3.

Fig. 4.

Figs. 2, 3, and 4. Roentgenograms taken of patient in the supine position before and after a total of 50 pounds of leg traction was applied. Needles were placed in the fourth and fifth lumbar vertebrae and the sacral arch. No alteration in the distance between the needles or angulation was observed when compared before and after leg traction was applied to this patient in the waking state after 5, 10, and 20 minutes.

of traction, with 25 pounds on each leg. The foot of the bed was raised to provide counter-traction. The x-ray films revealed no change whatever in the distance between the points of the 3 needles, or in their angulation (Figs. 2, 3, and 4).

Still another type of observation was carried out in 1 case, utilizing electromyograms to determine which muscles were affected by traction. The patient was fully awake and co-operative. Electrodes were applied to the skin overlying the following muscles: right and left abdominals, lumbar, gluteal, quadriceps, hamstrings, extensors, and flexors of the leg. Traction of 50 pounds was then applied to both legs and records were taken. The lower leg muscles revealed the most marked response, but short-lived, mild contractions were occasionally seen in the quadriceps or gluteal groups. The lumbar and abdominal muscles did not show any significant electrical responses.

DISCUSSION

It appears clear from these observations that, in typical cases of ruptured lumbar intervertebral discs, when traction was applied to one or both legs there was no demonstrable reduction of the herniation or a distraction of the adjacent vertebrae, whether the patient was awake or anesthetized, supine or prone. It could not be demonstrated that leg traction had any effect on the paraspinal muscles.

These observations are in no way a reflection on the value of conservative treatment in the management of ruptured lumbar discs. Indeed, it is our custom to insist on bed rest for at least 3 weeks before surgical removal of the disc is considered, and we firmly believe that all conservative measures should be utilized before operation is resorted to.

SUMMARY

1. Observations of ruptured lumbar intervertebral discs exposed at operation and measurements between fixed landmarks on adjacent vertebrae failed to demonstrate any perceptible change when as much as 25 pounds of skin traction were applied to one leg or 50 pounds to both legs.

2. In an unanesthetized subject in the supine position, no change of relative position or angulation between 3 needles inserted into the bodies of the fourth and fifth lumbar and first sacral vertebrae could be demonstrated by x-ray examination as a result of the application of leg traction.

3. Electromyograms demonstrate action currents in the muscles of the leg, less marked in the thighs and gluteal regions and not in the paraspinal and abdominal muscles, when traction is applied to the legs.

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POSTOPERATIVE INTESTINAL OBSTRUCTION

WILLIAM S. McCUNE, M.D., F.A.C.S., and JOHN M. KESHISHIAN, M.D.,
Washington, District of Columbia

ALTHOUGH the clinical characteristics of intestinal obstruction are familiar to the medical profession, the recognition of this complication in the ly postoperative period is difficult. Masked analgesic drugs, the symptoms may be mild totally absent. Distention and vomiting y be mistaken easily for the minor degree of is which is of common occurrence during first few days after abdominal operations. is not surprising that although most au- rs have indicated a steady lowering of the rtality rate due to intestinal obstruction in neral, Zaslow was able to report 7 deaths m postoperative mechanical obstruction lowing appendectomy alone. This number been augmented further by reports from ner sources. In the hope of adding to the rmation provided by these authors, this up of cases has been collected from several ashington hospitals over the 5 year period m 1947 to 1951 inclusive.

Forty-six cases of intestinal obstruction re recorded which occurred during the 15 ys immediately following operative proce- res of various kinds. Thirty-five of these re of mechanical obstruction and 11 of ralytic ileus. Although all of the cases were cluded which could be found under these agnostic titles, it seems obvious that in ny instances minor degrees of paralytic eus were not recorded as complications. This may also have been true of certain cases of mechanical obstruction which were relieved by conservative measures alone.

MECHANICAL OBSTRUCTION

Mechanical obstruction was due to a number of causes (Tables I and II), of which generalized adhesions, or those whose site was not stated or unknown, accounted for 34 per cent, adhesions at the operative site, 26 per cent, intestinal incarceration in peritoneal defects, 29 per cent, and failure of intestinal anastomoses to function, 11 per cent (Fig. 1). Only 12 of the patients were over 50 years of age. As clearly as could be determined the symptoms due to obstruction made their first appearance at periods varying from 2 to 15 days after operation. When the obstruction was due to generalized adhesions, the onset of symptoms was variable; when it was due to localized adherence of a loop of bowel to the operative site, the symptoms began in all instances between the second and seventh postoperative day. When a loop of intestine had become incarcerated in a peritoneal hiatus (such as a partial wound dehiscence, under an unreperitonealized ureter or in the breakdown of a newly formed pelvic floor) symptoms usually began between the second and seventh postoperative day. In one instance, in which a loop of intestine had become incarcerated and adherent in a peritoneal defect left during repair of a femoral hernia, no symptoms were noted until the thirteenth day. In the 3 cases in which small intestinal anastomoses failed to function, abdominal pain and distention began on the fourth day, although obstruction of a sigmoid anastomosis did not become apparent until the ninth day after resection.

The three symptoms found with the greatest regularity in postoperative mechanical obstruction were pain, vomiting, and distention (Table III).

Pain in the early postoperative period is difficult to evaluate. Papper has demonstrated that one-third of all patients have no significant pain after abdominal operations, while in two-thirds it varies in intensity from mild to severe discomfort. Morphine and other analgesic drugs can so mask this symptom at times that it becomes of little value in the differential diagnosis of mechanical obstruction. Nevertheless, in the majority of cases in this series (69 per cent), the charac-

From the Department of Surgery, The George Washington University School of Medicine, Washington, D.C.

TABLE I.—POSTOPERATIVE INTESTINAL OBSTRUCTION

Operative procedure	Mechanical No. cases	Paralytic No. cases
Pelvic operations	11	5
Intestinal resections	10	
Appendectomy	3	1
Lysis adhesions	3	
Exploration stab wounds	2	
Gastrectomy	1	2
Lysis adhesions and intestinal resection	1	
Abdominoperineal resection	1	1
Herniorrhaphy	1	
Ureteral transplantation	1	
Ligation vena cava	1	
Normal delivery		1
Eye operation		1
Total	35	11

teristic regularly recurrent colic, accompanied by peristaltic rushes (recorded in 57 per cent), gave a valuable clue to the correct diagnosis. "Gas pains" are more generalized, lack rhythmicity, and are not usually accompanied by peristaltic rushes which end in high pitched "tinkles." Incisional pain is constant except when accentuated by movement and usually diminishes in intensity daily except in the presence of an incipient wound infection.

After recovery from the postanesthetic nausea, vomiting occurred in 80 per cent of the patients with obstruction. It was late in onset in low ileal or large bowel obstructions, but, particularly in elderly patients in whom pain was not a prominent symptom, its persistent recurrence whenever gastric suction was discontinued provided reliable evidence of the presence of a mechanical block.

TABLE II.—POSTOPERATIVE MECHANICAL OBSTRUCTION

Sites of obstruction		No. of cases
Peritoneal hiatus		10
Partial wound dehiscence	7	
Pelvic floor dehiscence	1	
Femoral hernia defect	1	
Unperitonealized ureter	1	
Obstructed anastomosis		4
Adhesions (generalized or site unknown)		12
Adhesions (operative site)		9

Some degree of distention occurred in 86 per cent of the patients with obstruction. This is evidence of the fact that there were very few instances of higher intestinal obstruction in the series. The degree of distention often was not great but was sufficient to be definitely abnormal several days after operation.

The prevalent belief that the passage of gas or bowel movements is proof of the absence of obstruction is contradicted by the fact that in 40 per cent of the cases, some gas or fecal matter had been passed by rectum. In several instances, this had been of repeated occurrence and led to delay in the institution of definitive therapy. Possible explanations for this apparent paradox are the presence of gas and fecal matter in the colon at the time the obstruction occurs, the introduction of air with enemas, and errors in recording on the part of hospital personnel. The passage of large amounts of gas, however, with concomitant relief of distention was usually indicative of at least partial release of the obstruction.

The most valuable aid, both in the diagnosis of obstruction and in the differentiation between mechanical and paralytic ileus, was found to be frequent use of x-ray films and their interpretation by skilled roentgenologists. Roentgenograms were taken in all but 1 case and indicated obstruction (either paralytic or mechanical) in all instances. In all but 6 cases a definite diagnosis of mechanical obstruction was made, and in only 1 case was there an erroneous differentiation of paralytic instead of mechanical ileus reported. Films were taken in the supine and standing positions. The most important criterion for the diagnosis of mechanical small bowel obstruction was the presence of distended loops of small bowel but absence of any gas in the large intestine (Fig. 2). Confirmatory evidence was the presence of fluid levels in the upright film. On the other hand, if enemas had not been given recently and gas was evenly distributed between the small and large intestine, paralytic rather than mechanical ileus was indicated (Fig. 3). Portable abdominal films are of no value in demonstrating intestinal distention. Furthermore, it must be remembered that loops of small intestine are sometimes dilated by fluid rather than gas, and cannot be visu-

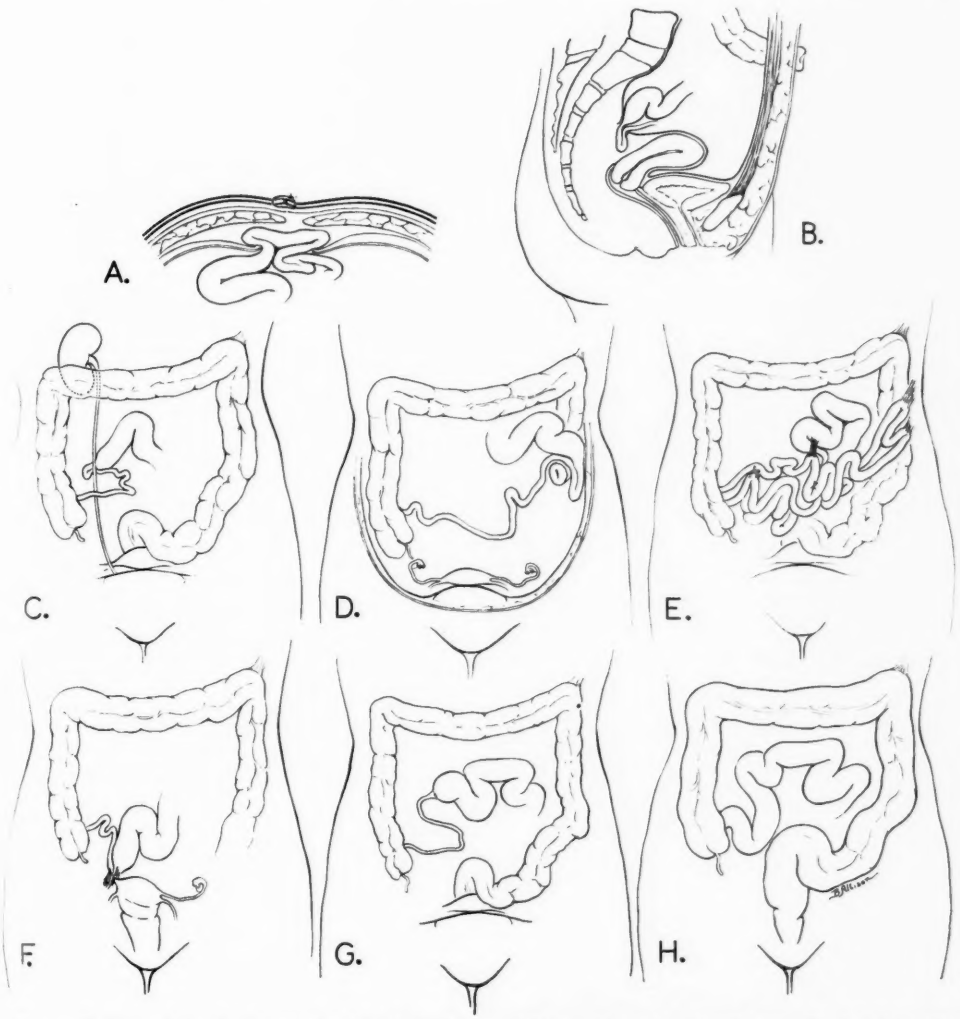

Fig. 1. Common sites of postoperative intestinal obstruction: A, partial wound dehiscence; B, separation of pelvic peritoneal floor; C, unreperitonealized ureter; D, unobliterated lateral gutter; E, generalized postoperative adhesions; F, adhesion at operative site; G, generalized postoperative adhesions; H, generalized adhesions.

alized in scout abdominal films. Although small amounts of thin barium, passed through a Miller-Abbott tube, have been used occasionally for the diagnosis of obstruction, this practice is fraught with considerable danger and its general use should be condemned.

Temperatures tended to be higher in paralytic than in mechanical ileus as noted by Zaslow, but some elevation at the time symptoms of obstruction became prominent was more common in the latter than in the former. The white blood count was elevated above 10,000 in approximately half of the cases of simple mechanical and paralytic obstruction. Neither the temperature nor blood count, therefore, proved of any value either in the

Fig. 2. Postoperative mechanical obstruction due to nonfunction of an end-to-end anastomosis. Distention of small intestine. Absence of gas in large bowel.

diagnosis of simple obstruction or in the differentiation of its types.

PARTIAL WOUND DISRUPTION

In 7 cases (20 per cent) of this series obstruction, partial or complete, was caused by the protrusion of a loop of intestine into an unrecognized partial disruption of the inner layers of the abdominal wound. Symptoms became apparent between the fifth and ninth postoperative day, and consisted in vomiting in all instances, often profuse with varying degrees of distention, and with or without abdominal pain. Since it has been shown that wound disruption is more common in patients suffering from cancer or malnutrition and often in those of advanced years, such individuals may be in a more or less critical condition when the partial wound disruption occurs. Careful inspection will sometimes reveal some puffiness of the wound area without evidence or induration and more than the usual degree

TABLE III.—POSTOPERATIVE INTESTINAL OBSTRUCTION

Symptoms and signs	Mechanical			Paralytic		
	No. cases	Per cent	Not recorded	No. cases	Per cent	Not recorded
Total cases	35			11		
Distention	30	86	2	10	91	
Vomiting	28	80	3	6	55	2
Pain	24	69	7	9	82	2
Fever	21	60	6	7	63	
Peristalsis present	20	57	9	4	27	5
Local tenderness	16	40	7	2	18	4
Bowel movements or gas	16	40	4	4	36	2
White count above 10,000	16	40	7	5	45	2

of local tenderness. It may be several days from the onset of symptoms before telltale serosanguineous fluid appears on the dressing and the skin itself begins to separate. On resuturing such incisions the surgeon is often surprised to find a dilated loop of bowel adherent between the edges, indicating that it has been in that location for several days. Although distention is usually regarded as causing the disruption, it is certain that in some cases, at least, early partial disruption causes obstruction and distention. The best guide to the diagnosis of this condition is alertness on the part of the surgeon. Once suspected, a lateral x-ray film of the abdomen will sometimes reveal the distended loop of bowel in the abdominal wall.

TREATMENT AND RESULTS

Reoperation was performed in 29 (83 per cent) of the cases of mechanical obstruction, and 6 were treated conservatively.

Conservative treatment consisted in intestinal intubation, enemas, oxygen inhalation, parenteral fluids and electrolytes, and transfusions when indicated. Such treatment was abandoned in favor of surgical intervention if within a few hours the obstruction was not overcome as evidenced by relief of pain and distention, and the passage of a significant amount of gas into the colon by x-ray examination.

Intestinal resections were performed in only 4 cases. Of the 4 patients all survived but 1

with recurrent small bowel obstruction caused by adhesions with volvulus and infarction of the obstructed loop. Two other patients died, one 41 days after a ureteral transplantation for carcinoma of the bladder, complicated by wound disruption and obstruction; and 1 patient for whom an exploratory operation was again performed because of small bowel obstruction due to malignant implants from resected carcinoma of the transverse colon. The total mortality in postoperative mechanical obstruction was 8.5 per cent.

PARALYTIC ILEUS

Eleven cases of postoperative paralytic ileus are included in this report. Distention occurred in all except 1. Vomiting was recorded in only 55 per cent and pain in 82 per cent. The pain was not as severe and rhythmic. Cramping was not reported in any of the cases. It should be emphasized, however, that mechanical obstruction sometimes occurs with little or no pain and that neither this nor any other single symptom can be relied upon for the differential diagnosis. Fever, usually higher than in mechanical obstruction, was present in 3 per cent of cases, local tenderness was rare, and audible peristalsis reported in only 4 patients. In 1 of these, however, it was of normal intensity and pitch. Roentgenograms were taken in only 6 of the 11 patients. In 4 the correct diagnosis was made; in 1, differentiation between the types of obstruction was not made. In another a diagnosis of a mechanical block was made by x-ray examination but at operation (the only one in this group) it was evident that the symptoms were due only to paralytic ileus. There was 1 death from acute ileus with dilation of the stomach following a hysterectomy for a huge fibroid tumor of the uterus.

Fig. 3. Postoperative paralytic ileus showing distention of both large and small intestine.

DISCUSSION

The most important factor in the diagnosis and successful management of intestinal obstruction during the early postoperative period is awareness of its possible presence by the surgeon. It is often erroneously believed that, since minor degrees of ileus are of common occurrence during the first few postoperative days and usually disappear after the first enema, all distention occurring during this period can be managed successfully by conservative means. The danger of this point of view is emphasized by the similarity of symptoms of mechanical and paralytic ileus in this series of cases, by the facts that 1 patient died of paralytic ileus as early as the fifth postoperative day, and that the only death due to resection of gangrenous bowel in mechanical obstruction occurred after a delay of treatment of 10 days.

The 3 most valuable clinical characteristics of postoperative mechanical obstruction are rhythmic pain, vomiting, and progressive abdominal distention not relieved by enemas. In the presence of any one of these, x-ray films of the abdomen in the recumbent and standing positions should be taken and interpreted by a skilled roentgenologist. If 2 of the 3 are present, mechanical obstruction must be presumed to be present until conclusively ruled out by roentgen studies or by the repeated passage of large amounts of gas by rectum. If evidence of mechanical obstruction is present and confirmed by x-ray studies, conservative treatment by intestinal intubation

is satisfactory only if it results in release of the obstruction within a few hours, as evidenced by relief of pain, decrease in the output of the intestinal tube, persistent passage of significantly large amounts of gas from the small into the large intestine as demonstrated by x-ray examination, and/or its passage by rectum with or without the aid of enemas. If any doubt exists that the obstruction has been relieved, early operation is indicated. It is significant that the operative findings in such cases often reveal more advanced obstruction than had been anticipated from the symptoms and signs alone.

SUMMARY

Forty-six cases of intestinal obstruction, occurring during the first 15 days after operation, are presented. Thirty-five were of mechanical obstruction, and 11 of paralytic ileus. In the former group, 6 were treated conservatively, and 29 by reoperation, with a mortality of 8.5 per cent. In the latter group, all but 1 were treated conservatively with a mortality of 9 per cent. The most important clinical characteristics of mechanical obstruction are rhythmic pain, vomiting, and distention. The most important diagnostic aids are the use and skilled interpretation of standing and recumbent x-ray films. Surgery is indicated in mechanical obstruction except in those cases which are relieved promptly by conservative measures.

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TREATMENT OF ESOPHAGEAL VARICES BY TRANSESOPHAGEAL OBLITERATION

GEORGE CRILE, JR., M.D., F.A.C.S., Cleveland, Ohio

IN 1950, I reported preliminary results in a group of 7 children and young adults who had bled frequently and severely from esophageal varices and who had been treated by transesophageal ligation of the esophageal veins. These patients had normal livers, and the varices were the result of a congenital block of the portal or splenic vein.

Since this report was published, we have had experience with 2 additional cases and have followed the original 7 patients from 33 to 48 months since operation. The results remain excellent, and only 2 of the 9 patients have bled since operation. One of these had 2 small hemorrhages soon after the operation was performed and has had none since. The other has had several episodes of bleeding, but this has been associated with severe abdominal pain and a demonstrable gastric ulcer. It appears, therefore, that transesophageal ligation of esophageal varices is a simple and safe method of dealing with esophageal varices that are secondary to extrahepatic blocks of the portal or splenic vein, and that in this group of cases there is no indication for the more extensive and dangerous procedures which have been advocated in the past.

At the time that the original group of cases was reported we were unaware that similar techniques had been employed, but it has since been brought to our attention that Doctor Boerema, of Holland, performed transesophageal ligation of varices as an emergency measure to control bleeding.

RATIONALE OF OBLITERATION OF ESOPHAGEAL VARICES

The operation of transesophageal ligation of esophageal varices is much like that of hemorrhoidectomy. The 3 large veins look exactly like the 3 large groups of hemorrhoids. After their obliteration the control of bleeding appears to be as prolonged and as complete as after hemorrhoidectomy.

Although dilatation of the hemorrhoidal veins is probably due to increased pressure in the portal or hemorrhoidal system of veins, we do not approach this problem by attempting to reduce the pressure. Perhaps the pressure in the hemorrhoidal veins would be reduced by anastomosing the inferior mesenteric vein to a systemic vein, but even if this were done it is likely that, if the hemorrhoids were large, they would continue to fill with blood and to bleed after trauma or with straining. The veins must be obliterated surgically before the bleeding is controlled.

Although hemorrhoids occasionally may recur after removal, the recurrences are more apt to be the result of an incomplete operation than of formation of new channels. Since a good hemorrhoidectomy usually affords permanent relief, no one gives serious consideration to the possibility of removing the rectum to control bleeding from hemorrhoids. If bleeding from esophageal varices can be as readily controlled by obliteration of these veins, it is hoped that resection of this area will be as unnecessary as removal of the rectum.

When esophageal varices are large and of long duration, the walls of the veins are extremely thin and anastomotic channels have developed between the esophageal veins and those of the azygous system (Fig. 1). These large channels are easily visible when the esophagus is exposed. Shunt operations which correct the portal hypertension cannot be expected to cause complete regression of the decompensated esophageal veins whose communications with the azygous system are not protected by valves. Hence, even if all communications with the portal system were cut or even if the pressure in the portal system were reduced to normal, the veins would still fill with blood and would still bleed if traumatized or ruptured by the increase of pressure

From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

DATA ON 9 CASES OF BLEEDING ESOPHAGEAL VARICES

Case	1	2	3	4	5	6	7	8	9
Age, years	23	13	13	30	21	13	20	25	24
Sex	F	F	M	M	M	M	F	M	F
Age at first bleeding, years	13	10	4	18	15	11	15	25	16
Age at splenectomy, years	16	11	5	19	21	14	10	25	16
Condition of liver*	N	N	N	N	N	—	N	N	—
Site of block†	S	S	P	S	S	—	S	S	—
No. of injections of varices	60	10	0	1	0	0	6	5	1
Devascularization of stomach and vagotomy	Yes	Yes	Yes	No	No	No	Yes	?	No
Total No. of transfusions	124	50+	12+	13	42	312‡	100+	47	5
No. of hemorrhages per year before ligation	23	19	17	4	8	30	7	6	2
No. of months without bleeding since ligation	See footnote §	45	43	44	36	33**	42	21	6
Disappearance of varices on esophagoscopic examination	Yes	Yes	—	Yes	—	Smaller	—	—	—
Disappearance of varices on roentgenograms	Yes	Yes	Yes	—	Yes	Smaller	Yes	—	—

* N indicates normal.
** Patient had huge varices involving the lower half of the esophagus. He bled twice soon after operation. None since.
† S indicates splenic vein and P portal vein.
‡ Patient had packing of mediastinum 3 years before operation, without benefit.
§ Eighteen months after operation patient developed severe abdominal pain and bled several times apparently from a large ulcer that developed in the stump of the denervated and devascularized stomach. No recent bleeding since 48 months after original operation.

incident to straining. Hence it would appear that the conventional indirect attacks on esophageal varices are of value chiefly in early cases or prophylactically before the varicosities are well developed.

The direct method of attack by injection is subject to the same pitfalls as injections of varicose veins of the saphenous system. Although small channels may be obliterated successfully, larger ones either do not thrombose or are apt to recanalize. Certainly no benefit of long duration can be expected after injection of large veins.

Resection of the involved area of stomach and esophagus is a rational approach provided there is no tendency to re-establish anastomotic channels connecting with the portal system. Time alone will answer the question of the effectiveness of this form of treatment. The chief disadvantages are its risk and the attendant morbidity.

Since 6 of the patients in this series were found to have no evidences of diffuse portal hypertension, we must assume that in many cases the block responsible for the Banti's syndrome in children and young adults is localized to the splenic vein and its tributaries. Since splenectomy had already been performed in all of these cases, splenorenal anastomosis was impossible. Portacaval shunts, moreover, would be of no value in the treatment of blocks limited to the splenic vein and would be impossible in those in which there is cavernous change in the portal vein. It seems, therefore, that shunt operations have little application in the treatment of extrahepatic blocks.

TECHNIQUES OF OPERATION

Exposure of the esophagus is obtained by resecting the seventh or eighth rib, and a longitudinal incision 1 inch in length is made in the mobilized esophagus about 2 inches above the cardioesophageal junction. The esophagus is held open with Allis' forceps and the 3 large groups of esophageal varices are immediately seen. Each of these in turn is obliterated by a running suture placed in the wall of the esophagus beneath the varix and then run on downward, each stitch being pulled up tight to obliterate the varix as it goes. The esophageal mucosa pulls up easily by traction on the suture, and the stitch can be carried down until gastric mucosa is reached. It is then returned in the same fashion and carried upward as far as the esophageal mucosa can be pulled down. In this way all the varices in the lower third of the esopha-

gus can be obliterated. This procedure does not cause any significant restriction of the lumen of the esophagus because it is merely the redundant mucosa overlying the varices which is sutured. The esophagus can then be closed longitudinally in layers without inversion.

DISCUSSION

This operation has not been applied to patients with cirrhosis of the liver, and it is not known whether simple obliteration of esophageal varices, without splenectomy or devascularization of the upper portion of the stomach, will suffice to control permanently the type of bleeding which results from a diffuse increase of portal pressure secondary to cirrhosis of the liver. We believe that the procedure is applicable as a life-saving procedure to patients who are bleeding acutely from esophageal varices, and in such patients we have demonstrated the bleeding points at the time of operation. The bleeding points were about 2 inches above the cardioesophageal junction, where there was a small area of ulceration about ½ centimeter in diameter, and in one case a clot was seen protruding from a large varix; in the other the varix was bleeding acutely.

One of the 2 patients who bled after operation was a boy of 13 who had bled innumerable times in the previous 7 years. He estimated that he had had 312 transfusions and that he was bleeding at intervals of 2 weeks. He has now been followed 33 months since operation, and aside from 2 episodes of tarry stools which occurred in the first few months after operation he has had no recurrence of bleeding.

The other patient was a woman 23 years of age, who had been bleeding intermittently since the age of 8 and had had more than 120 transfusions. This patient's spleen had been removed, her stomach had been completely devascularized, the vagus nerves had been severed, and she had had almost total gastrectomy performed. The patient, who had been bleeding at monthly intervals prior to operation, had no hemorrhages for 6 months, then developed severe abdominal pain and a demonstrable gastric ulcer in the denervated and devascularized stump of the stomach.

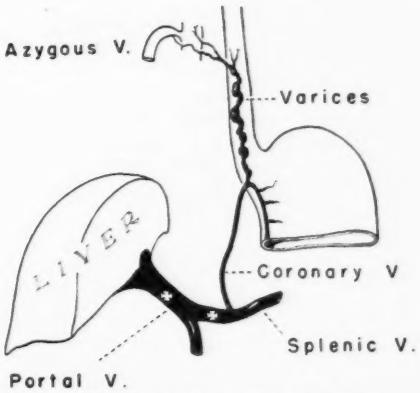

Fig. 1. Possible site of extrahepatic block and anastomotic channels with azygous vein sketched diagrammatically.

She has had several episodes of bleeding, presumably from this ulcer, but they have not been as severe as those which occurred prior to operation, and invariably have been associated with exacerbations of ulcer-like pain. She has had no pain and no hemorrhages in the past 8 months, during which time she has been following medical treatment for ulcer and has been "anointed by a faith healer."

The lower esophagus has been examined by esophagoscopy before and after operation in 4 cases, and in 3 of these 4 the varices, which were easily demonstrable prior to operation, were reported to be no longer visible. In the fourth case, they were reported to be much smaller and apparently deeper than prior to operation.

Roentgenograms of the esophagus showed large varices to be present prior to operation in 6 cases, and following operation they disappeared completely in 5 and appeared much smaller in the sixth.

Since most of the patients in this series have had their spleens removed at previous operations, it is not known whether the splenectomy and devascularization of the stomach contributed to the permanence of the effects of ligation of the varices.

SUMMARY

1. The rationale of transesophageal obliteration of esophageal varices is discussed, and it is pointed out that in patients with extra-

hepatic blocks true portal hypertension may not be present and that portacaval shunts may be impracticable or useless.

2. Radical operations, with resection of the lower esophagus and upper parts of the stomach, may be of value in patients with esophageal varices, but these procedures carry a high mortality and morbidity and should be avoided whenever possible.

3. Seven patients with esophageal varices secondary to extrahepatic blocks of the portal or splenic vein have been treated by transesophageal obliteration of esophageal varices and have been followed from 33 to 48 months since operation.

4. Five of the patients have had no further bleeding since operation, despite the fact that prior to operation they had been bleeding on an average of 15 times a year for several years and conventional methods of treatment had failed to stop the bleeding.

5. One of the 2 patients who has bled again appears to be bleeding from a gastric ulcer, and the other, who had been bleeding at 2 week intervals for several years prior to operation, has had no bleeding in the past 2½ years and had only experienced 2 small episodes in the first few months following operation.

6. Two other patients have been operated upon 21 months and 5 months ago, respectively, and have not bled since operation.

7. There have been no deaths or serious complications following operation in this group of cases except for the development of a gastric ulcer in 1 patient whose stomach had been subjected to partial resection, vagotomy, and devascularization.

8. This operation has not yet been tried in patients with varices secondary to cirrhosis of the liver, and it is not known whether or not it will control the bleeding in these cases.

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BLOOD IODINE LEVELS IN PREGNANCY AND ABORTION

KEITH P. RUSSELL, M.D., F.A.C.S., Los Angeles, California

THE thyroid gland has long been known to play an important role in all phases of the reproductive process. Many of the problems associated with the physiology and pathology of pregnancy have been related, directly or indirectly, to disorders of function or structure of the thyroid, and for some years extracts of the gland have been used, frequently empirically, in the treatment of certain of these disorders. Eastman has noted that there exists some evidence that reproductive difficulty may be the most sensitive indicator of thyroid deficiency and may be manifest long before other clinical signs. Various means have been devised to measure and evaluate the functions of the gland, and these in turn have been applied to studies of the complex aspects of infertility, abortion, premature delivery, malformations, and similar pathologic processes.

In general, there are at present four main methods available for measuring thyroid activity: (1) determination of the basal metabolic rate; (2) measurement of the protein-bound iodine of the blood serum; (3) measurement of the uptake of radioactive iodine (I^{131}); (4) assay of the circulating thyrotrophic hormone (TSH, or thyroid-stimulating hormone) of the pituitary.

Determination of the basal metabolic rate is, in actuality, determination of the oxygen consumption rate of the body at basal conditions. Since the thyroid gland is the metabolic regulator, the basal rate is an indicator of thyroid activity. However, it must be remembered that various extraneous factors of nonthyroid origin may influence or alter the bodily consumption of oxygen and thus affect the basal metabolic rate, so that the latter may not be considered a direct measurement of thyroid hormone. Many studies of the basal metabolism in pregnancy have been made. It has been well established that the rate normally shows a progressive increase beginning about the fourth month, attaining an average maximum of approximately plus 16 per cent at the end of pregnancy.

Clinical application of radioactive iodine depends upon the measurement of that fraction of the tracer dose collected by the thyroid gland; thus, the uptake of I^{131} is determined after its ingestion by mouth. The method is reasonably accurate, but, like the estimation of circulating thyrotrophic hormone, is not clinically feasible in everyday practice at the present time.

Repeated studies have established with certainty that the concentration of the protein-bound iodine of the serum is dependent upon the degree of activity of the thyroid gland, and hence may be interpreted as the most accurate measure of the amount of circulating thyroid hormone. As Peters notes, there is good reason to believe that most or all of the precipitable iodine of serum actually consists of thyroxine or active thyroid hormone. Unlike the basal metabolic rate, the protein-bound iodine is not concerned with oxygen consumption. The normal values for serum iodine lie between 4.0 and 8.0 micrograms per cent. In patients suffering from hyperthyroidism the level is characteristically above 8.0 micrograms, while in hypothyroidism it regularly falls below 3.5 micrograms. A number of factors may lead to false values. Any of the organic iodine compounds commonly used in radiologic diagnosis may elevate the protein-bound iodine, while the administration of mercurial diuretics will produce an abnormally low concentration. It should be stressed that only that portion of the iodine bound to protein is of clinical significance.

Blood iodine determinations have become increasingly utilized in practice, and have assumed major importance in clinical evaluation of the thyroid status of a given patient. Man, Peters, and associates (4–7) deserve credit for first directing attention to the critical relationships of the blood iodine levels in preg-

From the Department of Obstetrics and Gynecology, The Moore-White Clinic.

This study was financed by a grant from The Moore-White Medical Foundation.

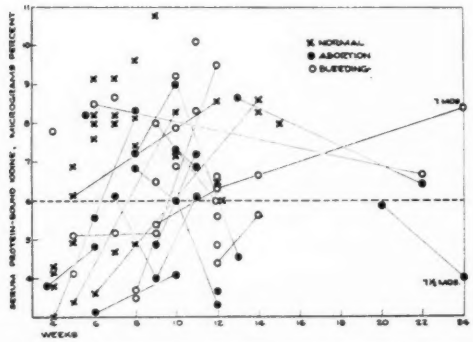

Fig. 1. Composite chart showing serum protein-bound iodine levels in the course of normal and abnormal pregnancy (60 patients, 83 determinations).

nancy. Their studies warranted the following general conclusions:

1. The serum protein-bound iodine (SPI) rises in early pregnancy and remains elevated until after delivery, returning to normal after a relatively short interval.

2. In normal pregnancy, the SPI usually reaches hyperthyroid levels without evidence of excessive thyroid activity, being regularly above 7.2 micrograms per cent in most cases.

3. The SPI remains below 6.0 in the majority of patients who abort before the sixteenth week of gestation.

The aforementioned workers have noted that the significance of these findings is obscure, although the increased levels are probably related to the thyroid hormone. Whether the hormone is merely produced in larger amounts during pregnancy, whether it is utilized less or more at this time with resultant altered levels, or whether the figures are an indication that the hormone is merely more firmly combined with the serum protein is not yet clear.

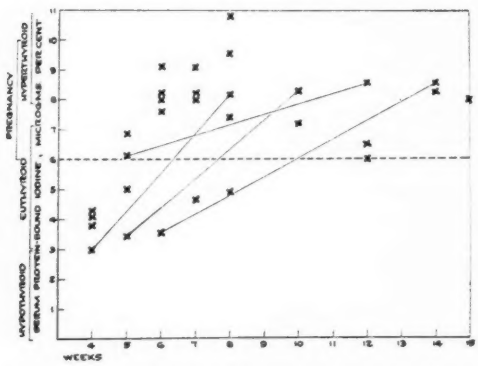

Fig. 2. Blood iodine levels in normal pregnancy. Crosses connected by lines represent repeated observations on same patient.

The present study was undertaken with the thought that further clinical studies of the protein-bound iodine of the serum and its possible relation to abortion would be of value. We desired to approach the problem as it exists in private practice, to determine if possible whether isolated serum iodine determinations would be of aid in predicting which patients might abort, and whether these latter could be segregated from those with a more favorable prognosis. It was our hope that certain gains by serendipity might become available as this clinical research was pursued.

METHOD

Until recently the laboratory procedures for measurement of the serum protein-bound iodine have been difficult and such determinations are not yet available in some hospitals. Barker's method has been widely accepted because of its high degree of accuracy. Connor and co-workers have recently presented a simplified technique for this determination. In the present series, the protein-bound blood iodine was determined by a modified Chaney distillation method in which the precipitated protein was digested, distilled, and the quantitative color reaction developed with ceric sulfate.

MATERIAL

This preliminary report is concerned with the results of the study of 60 patients on whom one or more serum protein-bound iodine determinations were made. Twenty-six of these patients pursued essentially normal courses during that period of their pregnancy under survey and may be considered as exhibiting the usual range of variation in the level of serum iodine during normal pregnancy. Of the remaining 34 patients, 13 are known to have aborted during the study, while the remaining 21 suffered from vaginal bleeding of

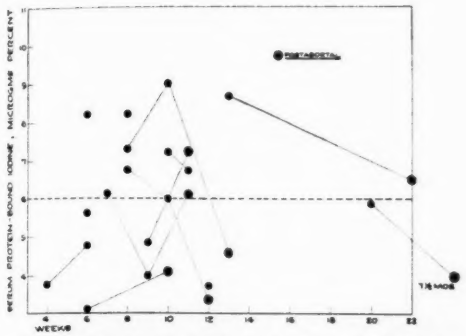

Fig. 3. Blood iodine levels in abortion. Encircled dots represent postabortal determinations.

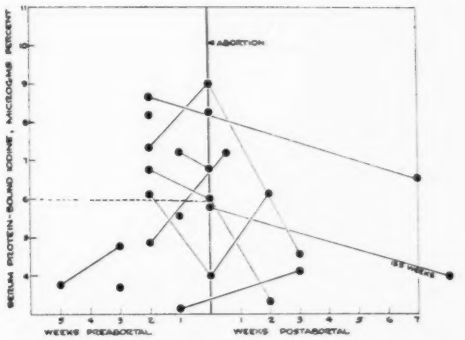

Fig. 4. Blood iodine levels in abortion. Levels shown in relation to time of abortion.

greater or lesser extent sometime during the first half of pregnancy, but did not abort.

A total of 83 serum iodine determinations were made on the 60 patients. A composite chart exhibiting the results is shown in Figure 1.

RESULTS

Studies of the normal pregnancies revealed that all determinations were in the upper euthyroid or hyperthyroid range by the *tenth* week of gestation. None was below the normal level of 6.0 micrograms established for pregnancy by Peters, Man, and co-workers by this period of gestation, which is somewhat earlier than the findings of these workers. However, those determinations performed at the fourth week, numbering 4, were 4.2 or below. From this time forward, on the other hand, there was a rapid rise in the level, so that 2 weeks later (at the sixth gestational week), the average of 8 levels was 6.6 micrograms, well above the lower normal level for pregnancy. The highest level found in normal pregnancy was 10.8 micrograms. None was found in the hypothyroid range, and the 3 patients who initially exhibited levels of 3.5 or less showed a rise to 8.0 or better at the eighth, tenth, and fourteenth weeks respectively (Fig. 2).

Findings in the 13 patients who aborted are shown in Figures 3 and 4. It will be seen that there is no consistency of results in these cases, although a tendency for low levels definitely exists. It is apparent that the large number of elevated determinations in these patients would invalidate an isolated serum iodine reading as being of prognostic value in cases of abortion. Approximately half of the initial determinations were above the level of 6.0 micrograms. Even when the abortion was clinically inevitable, the serum iodine was frequently still elevated, an indication that the blood iodine concentration is not always an important factor in abortion.

Blood iodine levels in patients who exhibited bleeding during the first trimester, but did not abort, are shown in Figure 5. The majority of these patients exhibited elevated serum iodines and the general level was higher than that of the abortion cases. Only 2 patients had readings below 4.0 micrograms, and 1 of these showed a prompt rise to 9.5 in a

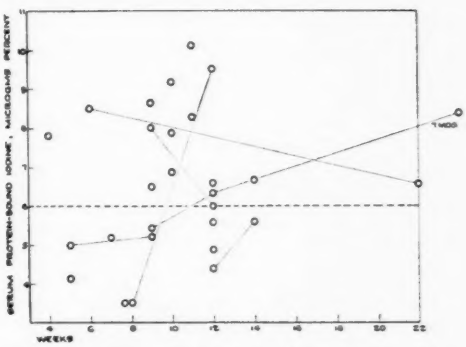

Fig. 5. Blood iodine levels in bleeding cases without abortion. Connected circles represent repeated observations on same patient.

subsequent determination. However, the fact that 7 of these patients had initial levels of 5.0 or less would indicate again that an isolated iodine determination is not a completely reliable prognostic figure in a patient who may be threatening to abort. It is significant, on the other hand, that none of the higher readings exhibited a fall below 6.0 in these cases. The general tendency was upward in the levels within this group. This is in contrast to many of the abortion cases, in which a higher level was found to show a tendency to decline as the abortion occurred.

One patient upon whom a therapeutic abortion was performed was studied. The case is of interest because it illustrates the usual course of serum iodine levels during and following pregnancy. At 8 weeks' gestation the level was 7.3 micrograms. Two weeks later, just prior to therapeutic interruption of the pregnancy for hypertensive disease, the level was 9.0 micrograms. Three weeks following abortion, the reading had fallen to 4.5.

Although the latter case is an example of the usual picture, there are enough deviations from normal in the complicated cases to make the serum iodine determination relatively unreliable as a prognostic aid. In our hands, the clinical evaluation of the patient was more nearly accurate in this regard. One cannot, however, disregard the statistically important tendency toward higher iodine levels in normal pregnancies, and the more frequent occurrence of lower levels in cases of abortion. In this respect, the present study has had the effect of confirming in general terms the original findings of Man, Peters, and associates on serum precipitable iodine levels associated with pregnancy and abortion. It is hoped that further studies will reveal methods of elevating those iodine levels which remain abnormally low and are associated with abortion.

SUMMARY

A preliminary report on the results of a study of serum protein-bound iodine levels in normal pregnancy and abortion is presented.

Sixty patients were studied, of whom 26 pursued normal pregnancies, 13 aborted, and 21 exhibited bleeding in the first trimester but did not abort. Eighty-three iodine determinations were performed in this series.

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EFFECT OF POLYVINYLPYRROLIDONE IN OBSTETRICAL CASES

A. C. POSNER, M.D., F.A.C.S., JOHN W. V. CORDICE, JR., M.D., and JOHN SCUDDER, M.D., F.A.C.S., New York, New York

DOES polyvinylpyrrolidone cross the placental barrier? If so, what effects are to be observed in the fetus or newborn infant? What changes are to be noted at parturition? Are cases of obstetrical shock benefited?

CHARACTERISTICS OF POLYVINYLPYRROLIDONE

Polyvinylpyrrolidone is the cumulation of 15 years of research in an effort to produce a cheap and satisfactory "blood extender," for the emergency treatment of traumatic and hemorrhagic shock.

PVP, a hydrophilic polymer, developed in Germany prior to World War II, is synthesized from ammonia, acetylene, and water. It is a homogenous white powder, readily soluble in water, chemically inert, and in the ultracentrifuge gives a characteristic picture and sedimentation constant. When mixed with plasma and subjected to electrophoresis in a Tiselius cell, PVP gives a characteristic picture and shows no mobility. It does not react with the plasma proteins. The molecular weight of the present material varies between 10,000 to 100,000 with the average being around 45,000. For clinical use it is dispensed as a 3½ per cent solution in Ringer's. In this concentration, it is slightly hypertonic and develops a colloidal osmotic (oncotic) pressure of approximately 400 to 460 millimeters of water. In this state, its viscosity in relation to water at 37 degrees C. is about 2 and as such is slightly hyperviscous in comparison with plasma.

Biologically, PVP is nonantigenic and nonallergenic in man. Repeated injections do not produce sensitivity. The hematopoietic system as well as the blood coagulation mechanism are not affected by infusions of this material at the present concentration.

No difficulty is encountered with blood typing and Rh determinations. The sedimentation rate of erythrocytes (ESR) is accelerated as is seen in the additions of other macromolecular substances. There is moreover, no interference with the respiratory function of the red blood cells.

PVP-macrose both increases and maintains circulating blood volume as judged by the blue dye (Evans) from 12 to 24 hours. PVP is excreted by the kidney rapidly during the first 6 hours with elimination of 60 to 70 per cent within the first day. The residue is not metabolized but is taken up with readiness by the reticuloendothelial system. No deposits have been seen in the tissues and there have been no sequellae.

During World War II, PVP had a wide clinical use on the German battlefields and in the treatment of burn, wound, and hemorrhagic shock. Equally successful was the civilian experience in the bombed cities. Since the war, PVP continues to be widely used on the European continent by the Germans, French, and Italians.

The present current interest in polyvinylpyrrolidone is for the stock piling of a "blood extender" that is safe, that is not affected by extremes in climate and that does not transmit the virus of homologous serum jaundice because in its manufacture PVP is autoclaved without losing any of its effectiveness. With age the solution develops a yellow tinge but still maintains its transparency.

POLYVINYLPYRROLIDONE AT PARTURITION AND IN OBSTETRICAL SHOCK

A study was conducted on the obstetrical service at the Harlem Hospital, New York, to assay the effects and results of PVP-macrose. Sixteen healthy females in labor were given 500 cubic centimeters of PVP-macrose (3.5 per cent polyvinylpyrrolidone in Ringer's solution). At the time of delivery, cord blood samples were examined for the concentration of PVP. In 13 patients, in whom satisfactory cord blood specimens were obtained, the concentration of PVP in micrograms per milliliter was plotted against the time elapsed between the infusion to the mother and the collection of the cord blood at delivery. These results are shown in Table I and Figure 1. The recorded blood pressures were taken before and after the infusion.

In 4 instances of obstetrical shock at Harlem Hospital following intrapartum and postpartum hemorrhage, an infusion of PVP successfully initiated replacement therapy until blood was obtained and definite surgical procedures carried out to stop the hemorrhage.

From the Departments of Obstetrics and of Surgery, Harlem Hospital, and the Department of Surgery, College of Physicians and Surgeons, Columbia University.

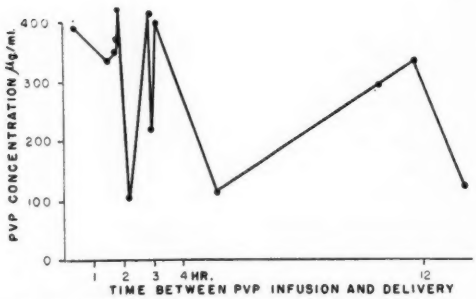

Fig. 1. PVP in cord blood following antepartum infusion.

At the Presbyterian Hospital, New York, one patient with ruptured ectopic pregnancy and one with incomplete abortion, both in profound shock from blood loss, were improved and blood pressure sustained by PVP until adequate quantities of carefully cross-matched blood were obtained from the blood bank.[1] Also in 2 other cases of shock from postpartum hemorrhage, PVP was employed successfully until blood was obtained. Table II gives pertinent data on these cases.

DISCUSSION

Our results amply confirm the work done by Klees in Germany and reported in 1943 on the use of polyvinylpyrrolidone in the treatment of obstetrical shock. We also substantiate the findings of Clerc, Mueller, and Schwalm who used PVP in both obstetrical and gynecological cases.

From the graph, no definite correlation is observed between the cord blood concentration of PVP and the time elapsing between the administration of PVP and the collection of the cord blood specimen. This may be due to the individual variation in placental permeability to PVP from patient to patient and to other factors. That it does enter the fetal circulation, however, is an established fact. No untoward effects were observed in any of the newborn infants in the study. All findings are in agreement with those of Pagani who previously reported the presence of PVP in the blood of the newborn after the mother had received an infusion of PVP prior to delivery.

[1]Since October 1, 1952, cross-matching of blood using the indirect Coombs' technique (antihuman globulin) has become mandatory at the Presbyterian Hospital so as to avoid reactions due to prior sensitization.

TABLE I.—CORD BLOOD STUDY OF PVP

Case No.	Patient	Bloodpressures beforeandafter 500 c.c. PVP-macrose infusion	Time elapsing between infusion and delivery hr.	min.	PVP cord blood level µg./ml.
1	M.B. 23 years Para 2 Gravida 4 #105	104/60 110/80	10	35	295
2	O.J. 35 years Para 1 Gravida 4 #119	114/84 120/90	2	58	220
3	A.G. 31 years Para 12 Gravida 11 #218	98/70 100/74	1	30	335
4	M.L. 22 years Para 3 Gravida 4 #260	138/90 134/88	1	48	420
5	J.W. 25 years Para 1 Gravida 2 #263	114/80 120/84	2	55	415
6	H.S. 21 years Para 0 Gravida 1 #264	120/82 120/84	1	47	370
7	F.B. 25 years Para 1 Gravida 2 #268	110/74 112/76	3	5	400
8	W.D. 20 years Para 1 Gravida 2 #275	130/80 128/78	11	47	335
9	J.A. 33 years Para 5 Gravida 6 #282	110/60 114/70		25	380
10	P.P. 24 years Para 0 Gravida 4 #902	120/80 120/80	1	45	350
11	E.R. 20 years Para 0 Gravida 1 #903	120/84 124/82	5	8	115
12	H.W. 26 years Para 1 Gravida 2 #917	112/70 118/72	13	21	125
13	M.S. 39 years Para 4 Gravida 5 #921	126/80 128/80	2	12	105

TABLE II.—OBSTETRICAL SHOCK CASES TREATED WITH PVP

Case No.	Patient	Diagnosis and cause of shock	Amt. of PVP c.c.	Other I.V. fluids	B.P. and pulse before and after therapy	Result
1	T.B. 23 years Para 1 Gravida 1 H.H. #52–6077	N.S.D. Labor prolonged and tiring to mother. Mild shock postpartum due to exhaustion and slight hemorrhage	500	None	90/40 96 120/80 88	Improved. Discharged on 7th postpartum day
2	V.B. 24 years Para 1 Gravida 1 P.H. #099424	Low forceps delivery with third degree tear and cervical laceration. Hemorrhage and mild shock	1000	500 c.c. whole blood	80/60 88 100/70 84	Improved. Still on ward
3	L.C. 17 years Para 1 Gravida 1 H.H. #52–7717	N.S.D. Postpartum hemorrhage. Possible thrombocytopenia	1000	1000 c.c. whole blood	94/70 108 104/76 84	Improved. Discharged on 8th postpartum day
4	C.F. 26 years Para 4 Gravida 5 P.H. #117553	Incomplete abortion, early acute hemorrhage	500	1000 c.c. whole blood during and after D and C	80/50 90 102/60 82	Improved. Discharged on 4th postoperative day
5	E.H. 21 years Para 1 Gravida 1 H.H. #5206744	Low forceps. Vulvar hematoma following pudendal block. Laceration from hematoma into vagina with severe hemorrhage	1500	1000 c.c. whole blood given slowly, although shock had already been controlled	66/44 122 120/75 112	Improved. Discharged on 8th postpartum day
6	R.L. 19 years Para 1 Gravida 1 P.H. #091441	Low forceps delivery. Hemorrhage from episiotomy and periurethral tear	500	500 c.c. whole blood	70/20 120 110/70 120	Improved. Discharged on 9th postpartum day
7	M.C.R. 31 years Para 1 Gravida 2 P.H. #113331	Ruptured ectopic pregnancy with severe hemorrhage	500 (in O.R.)	Upon admission 500 c.c. plasma 500 c.c. N-saline during operation after PVP 1500 c.c. whole blood 500 c.c. saline	0/ 0 very weak thready 120/90 108	Improved. Discharged on 11th postoperative day
8	R.W. 21 years Para 1 Gravida 1 H.H. #52–7708	N.S.D. Hemorrhage due to retained placental fragment which was removed manually	500	500 c.c. whole blood	60/30 118 100/60 100	Improved. Discharged on 9th postpartum day

N.S.D., Normal spontaneous delivery.

CONCLUSION

PVP-macrose diffuses across the placental barrier. No untoward effect was noted in either the mother or the newborn infant. The parturient case was benefited clinically by the infusion.

Six cases of obstetrical shock and 2 cases in which shock was due to hemorrhage occurring in pregnancy were controlled pending the arrival of compatible blood from the blood bank.

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WOUND HEALING IN THE UTERUS

ORVAN W. HESS, M.D., F.A.C.S., New Haven, Connecticut

AMONG the recent trends in the practice of obstetrics, two facts of significance have emerged which re-emphasize the importance of a clear understanding of the nature of the healing wound in the uterus.

In all parts of the nation an increasingly large number of pregnant women are presenting themselves for obstetric management who have had incised wounds of the uterus at one or more previous cesarean sections.

Secondly, there seems to be an increasing tendency for some obstetricians to permit vaginal delivery among this group of patients with the knowledge that such wounds have existed.

In both instances the pregnancy is complicated by a risk of rupture of the uterus, either before or during active labor, with its potentially high maternal and fetal mortality.

Attributable to the advent of antibiotic therapy, readily accessible blood banks, and improvement in operative and anesthesia techniques, there has been in the last decade an appreciable reduction in the maternal mortality and morbidity from cesarean section per se.

It has been stated that the mortality rate from cesarean section should be less than 1 per cent. Huber has reported 888 cases with a rate of 0.56 per cent while Dieckmann reported 0.24 per cent in his series of 4,497 sections completed in 1950. He believes that the maternal mortality rate should approximate 0.1 per cent. At New Haven Hospital, with 633 sections (1935 to 1944), the mortality rate was 0.31 per cent (11). No maternal deaths have occurred during more than 825 sections done at this hospital during the past 5 years. As a consequence of the greater safety of the operation there has been a broadening of the scope of indications for its employment, particularly in an attempt to eliminate difficult and traumatizing forceps operations.

From the Department of Obstetrics and Gynecology, Yale University School of Medicine.

For these reasons the incidence of cesarean section has increased from 2.1 per cent to 5 or 6 per cent of the total deliveries of all types in the larger clinics during the past 5 years. D'Esopo, in a review of the Manhattan hospitals, reported an increase from 4.1 per cent in 1941 to 6.2 per cent in 1948. In his tabulation of the data from 10 prominent hospitals, he recorded a variation in the incidence of cesarean section from 2.1 per cent to 7.1 per cent with an average of 4.9 per cent. On private services in some hospitals this has reached 9 to 12 per cent.

INCIDENCE OF REPEAT SECTIONS

During the same time that this increase in the total number of sections has occurred, there has been a relatively greater increase in the percentage of so-called "repeat sections." Reports from various hospitals indicate that these represent from 16.5 per cent to 43.4 per cent of all such patients. In at least 3 major clinics this percentage has increased from 20 to 30 per cent during the past 5 year period. At the New Haven Hospital, concomitant with a relative decrease in the incidence of *primary* sections since the adoption of the training for childbirth program on the University service, the percentage of repeat sections has increased from 20 per cent (1945) to a peak of 51 per cent (1951). Similarly, on the private service the percentage has increased from 18 per cent to 38 per cent during the period 1947 to 1952. Mack, in collaboration with the Detroit Health Department, in an analysis of that metropolitan area, found an increase from 18.3 per cent (1947) to 28.7 per cent (1950). The number of repeat sections performed in that vicinity had almost doubled in number in 3 years. Wilson reported from the New York Hospital that deliveries after section cases had increased from 1.1 per cent of all deliveries to 1.9 per cent (1944 to 1950), about twice as many.

Although it may be presumed that this trend will ultimately reach a plateau, a con-

tinued increase may be anticipated for some time and will include larger numbers of patients who have had multiple sections. This large group of patients, in whom the pregnancy has been terminated by a uterine incision, presents the obstetrician with a definite clinical problem which requires special consideration.

Statistical analysis of data from a large number of hospitals with respect to the indications for the primary section reveals that more than 30 to 50 per cent of patients had their first section for reasons which may be considered to have been of a temporary nature. Estimates indicate that patients in this category represent about 12.5 per cent of all cesarean section cases (D'Esopo, 12.5 per cent, Wilson, 12 per cent). This is substantiated by our findings at the New Haven Hospital (15 to 18 per cent). It is in the management of this group of patients, whose only essential difference from other multigravidas exists in their having had a previous incised wound of the uterus, that the obstetrician often finds himself facing the question of the type of delivery for his patient.

VAGINAL DELIVERY FOLLOWING SECTION

The concept, previously held, that cesarean section is mandatory has been challenged by a few observers. Recently recorded results of more than 629 (U.S.) and 678 (foreign) vaginal deliveries following one or more previous cesarean sections are now available in the literature. Although the vast majority of obstetricians prefer to deliver these patients abdominally it has been shown that, under carefully controlled conditions in selected cases, successful delivery has been achieved without serious complications. Regardless of the method of delivery elected by the obstetrician the decision will rest to a large extent on his concept of the strength of the uterine scar and its ability to withstand the strain of labor. It becomes apparent, therefore, that every effort should be made to assure the best possible healing of the uterine incision after section and to learn more about the physiologic process of healing.

Four major clinics have recorded their experience in following a series of patients who were permitted to deliver vaginally after previous cesarean section. In the conduct of this study, a careful and searching routine of management was set up. Careful evaluation was made of all factors relating to the status of the uterine scar and signs indicative of impending rupture. The character of the labor was closely observed, and adequate facilities were available for emergency surgery if indicated. Primary indications for the previous cesarean section were given careful consideration. In the majority of instances, vaginal delivery was allowed in patients whose previous section had been done for temporary indications. True cephalopelvic disproportion cannot be questioned as an adequate indication for a repeated section. Nevertheless it is of interest to note that a large number of patients (30 per cent in one series) previously operated upon for this reason were delivered vaginally. However, many of these patients had not had x-ray pelvimetry or an adequate trial of labor.

RUPTURE OF THE UTERINE WOUND

It has been postulated that rupture of the pregnant uterus occurs about once in every 2,000 deliveries. In his analysis of the literature on this subject, Brierton found that this condition occurred in 1:1,010 to 1:3,029 cases. Reporting on a series of 35,253 deliveries, Parker and Jones (Virginia hospitals) recorded 22 ruptures, an incidence of 1:1,602. Of these, 30 to 50 per cent will represent ruptures of scars of previous cesarean sections. In Brierton's review of 246 patients (Bellevue 1932 to 1947) carried to the last trimester of pregnancy after section, there were 7 ruptures (2.8 per cent) or 1:35.

In a group of 3,212 patients followed during pregnancy after having had a previous cesarean section, a total of 46 ruptures were found. This represents an average incidence of 1:70 with a variation of 0 to 1:17 and 1:30. The high frequency of occurrence of rupture of the uterine scar under these conditions has perhaps not been generally recognized.

Among the 629 vaginal deliveries after cesarean section reported in the U.S. literature, only 2 wounds, both of which were of classical type, ruptured while the patient was

undergoing active labor. This incidence of 1:315 in an admittedly small group of selected cases, compared favorably with the incidence of 1:70 of rupture in the larger group of repeat sections. Of the 46 ruptures which occurred in this latter group, although the majority involved wounds of the classical type, it is of interest that 11 (25 per cent) were of the low cervical variety. In view of the preponderance of previous lower segment incisions, this series supports the belief of many obstetricians that the wound of the classical type is more susceptible to rupture. In an analysis of 26 instances of rupture of the scar of previous section, Brierton found 19 classical scars and only 7 lower segment scars, that is a ratio of 2.7:1.

Wilson has recorded observations made at routine intrauterine palpation of previous section scars immediately following vaginal delivery. This highly commendable procedure will provide invaluable information otherwise unobtainable. Fifty-six per cent of 16 cases involving classical scars were found to exhibit significant defects of varying degree. Of 28 low transverse scars, only 2 (7 per cent) revealed defects. Although no complete ruptures were found in this study it is of interest that vaginal delivery was accomplished apparently without untoward clinical symptoms. One can only speculate with regard to the prognosis in the event of the strain of a future pregnancy. It is probable that some ruptures of occult type go unrecognized.

In an evaluation of this problem certainly the available statistics are insufficient to provide information which is conclusive, or perhaps even truly representative, of the application of the most recent techniques. During the past 5 years in many sections of the country, the incidence of subsequent rupture has been markedly lessened with reports of 1:150 and 1:200 now appearing in the literature. Indeed, in the group mentioned previously, it will be seen that several hospitals reported a complete absence of this accident in a fairly large number of cases. However, the high rate still existent in some areas suggests that greater attention should be given to the improvement of factors related to the healing of these uterine wounds.

THE HEALING CESAREAN INCISION

The histologic characteristics of the healing wound to a large extent reflect the strength of the scar. The type of tissue of which it is composed will govern its ability to withstand the effects of an ensuing pregnancy and the additional strain of labor. Most authors, during the past 30 years since the assertion by J. Whitridge Williams that union resulted from regeneration of smooth muscle, have directed their attention to the anatomic study of these scars. Later Schwarz and Paddock, after a review of scars of excised human uteri, reported that their findings indicated that healing was the result of proliferation of fibrous tissue. Two schools of thought, with healthy controversy, have thus developed around this issue. Less attention has been directed toward factors which may have a physiologic influence on the process.

The healing wound of the uterus following cesarean section is in some ways unique. The incision involves the wall of an organ composed of largely smooth muscle and, dependent upon its location, a variable amount of connective tissue. Mechanical factors are present which are not encountered in association with wounds of other regions of the body. Almost before reapproximation of the edges is begun, contraction of the incision begins following the extraction of the fetus. This is further enhanced by the action of oxytocic agents usually employed. In but a few days, the uterine body and the incision will have reduced more than one-half its original size. Although certain factors may interfere with this process, under normal circumstances of involution, the wound bearing area will approximate one-quarter to one-fifth of its original length. Thus an original longitudinal incision of 10 centimeters will have diminished to a scar of roughly 2 centimeters with further contraction to be anticipated during the secondary phase of healing. The transverse incision in the lower segment may be expected to undergo less rapid contraction. In addition, repair must take place, with its accelerated growth, in an organ undergoing the contraction and atrophy accompanying the marked proteolytic catabolism of the immediate postpartum stage.

Both types of tissue traversed by the incision are capable of participation in the healing process to a variable extent. The reparative process is not new to the uterus. Response of the uterine tissues to the growth hormones related to the cyclic changes of menstruation and during pregnancy are well known. The ability of smooth muscle fibers to undergo growth changes and to reproduce themselves has been demonstrated in several ways. Myomatous tumors are often observed to undergo rapid expansile growth as a result of myometrial proliferation. Smooth muscle fibers have been grown in tissue culture. In wounds of the mouse uterus Hooker was able to demonstrate regeneration of the smooth muscle layer while in other species we have noted mitosis and activity of the smooth muscle fibers adjacent to the site of the wound. However, the predominant reaction to injury noted during this phase of healing involves the appearance of fibroblasts and the production of a scar composed mainly of connective tissue.

During the course of a subsequent pregnancy the growth response of the muscle fibers follows with elongation and changed consistency of the individual cells. The area of scar tissue remains relatively static. It may undergo some slight change in consistency, perhaps similar to that noted in the softening of the fibromuscular cervix or of fibroids during early pregnancy. Gardner observed marked structural change in the pubic symphysis of the guinea pig after injections of estrogens, a process which may be analogous to some instances of separation of the pubis noted in the human during pregnancy. This suggests an influence of steroid hormones on collagenous tissues. However, growth and expansion during pregnancy involve mainly the adjacent myometrium with absence of appreciable gross change in the fibrous tissue component of the scar.

This may explain the frequent difficulty encountered in the attempt to locate the site of previous incision and the impression that the healing process has largely involved regeneration of smooth muscle alone. This may be particularly noted in the classic incision where a thick wall of myometrium has been traversed. A more dense scar may be found at repeat section where a transverse incision through the more fibrous lower uterine segment has been previously utilized. Incisions of the lower uterine segment rupture less frequently than those of the fundus. As an additional advantage, ruptures at this site are often incomplete without extrusion of uterine contents into the peritoneal cavity. This results in an appreciably higher fetal and maternal salvage.

The character of the scar may be altered by several factors. Infection, with its inflammatory reaction and prolonged exudative phase, may result in delayed healing. The common association of a history of a febrile postoperative course with wound disruption suggests a weaker scar. For this reason, liberal use of antibiotics is advised. In some instances, as in secondary healing, infection may be followed by a denser scar associated with firm adhesions which may make subsequent section technically difficult. In the closure of the cesarean incision, special care should be taken to control bleeding and avoid possible hematoma. Gross hematoma may interfere with prompt union and, when formed beneath the bladder flap, may become infected to drain through a uterine sinus at the site of the incision. When the incision has extended low behind the bladder, the latter may become incorporated in the healing process. During a later pregnancy, rupture involving the posterior vesical wall has been reported. All membranes and placenta should be removed. Interposition of these tissues between the wound surfaces will interfere with healing and favor infection. Principles governing the technical handling of wounds in other regions of the body should be observed. Better results may be anticipated when interrupted sutures of chromic catgut are used to approximate the myometrium. Owing to rapid involution and the tendency for sutures to loosen, there is less likelihood of strangulation of tissues and sutures should be tied snugly. The serosa should be closed by a separate row of sutures. The tendency to introduce too many sutures and too much catgut should be avoided. The use of nonabsorbable suture material is inadvisable since, as contraction of the uterus

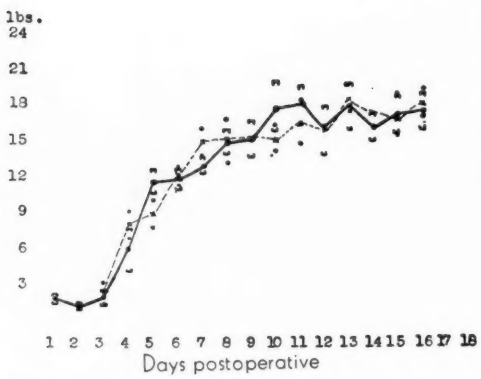

Chart 1. Curve of tensile strength, rat uterus. .—.—.—., mean of observations on standard diet (group 1). x- -x- -x- -x, mean of observations after estrogen (small doses) (group 2).

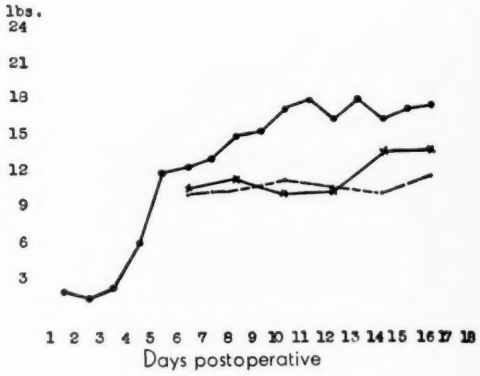

Chart 2. Curve of healing wound, rat uterus. .—.—.—., nonpregnant on standard diet (group 1). x—x—x—x, after estradiol propionate (large doses) (group 3). - -.- -.- - ., after progesterone (group 4).

occurs, there is a tendency for migration of sutures to form a persistent nidus of foreign body.

EFFECT OF HORMONES ON FIBROPLASIA

Much experimental data have been accumulated to determine the influence of various elements (age, diet, vitamins, inorganic substances) upon the rate of healing of wounds. However, the factors basic to the initiation and control of the reparative processes in the organism in response to injury remain obscure. Within narrow limits, in an animal maintained in a reasonably normal nutritional state and provided with adequate sources of protein, vitamins, and freedom from disease, the incised wound may be anticipated to undergo the healing process and regain strength with a high degree of constancy. Deficiencies of proteins and ascorbic acid have been clearly shown to result in poor healing. The evidence of effect of secretions of the various endocrine glands upon tissue metabolism and growth would lend support to the theory that such substances may play a role in the healing process.

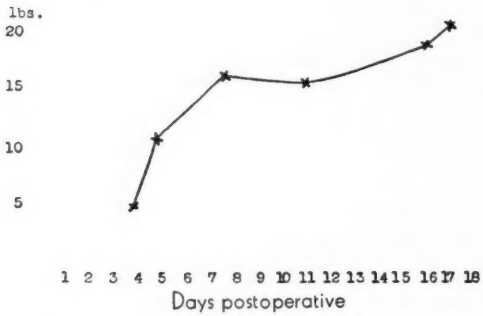

Chart 3. Curve of healing wound, rabbit uterus (after hysterotomy during pregnancy (group 5).

The growth-stimulating effect of the ovarian follicular hormone on the genital tract has been repeatedly noted. The reaction of the vaginal epithelium is striking as well as that of the endometrium where active mitosis, newly developed glands, and active proliferation within the stroma appear. Such growth may be produced in spayed animals whose genital tissues, atrophic from the effect of castration, have been restored to normal following injections of this hormone. In addition, many observations have been made concerning its growth effect on other body tissues. There is some evidence that connective tissue and the myometrium under conditions of excessive secretion of follicular hormone with unopposed action will undergo an abnormal response with production of fibromyomatous tumors as well as hyperplasia of the endometrium. In view of the fact that uninjured genital tissues undergo definite growth re-

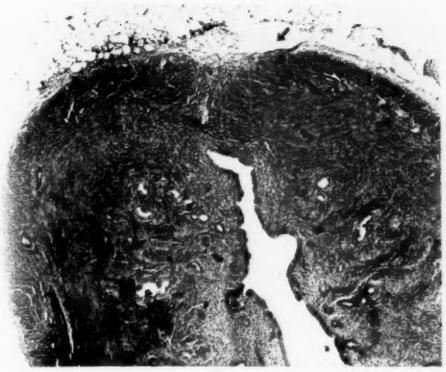

Fig. 1. Healing wound, rat uterus after 7 days. ×22. Endometrium regenerated. Fibroblastic tissue fills defect.

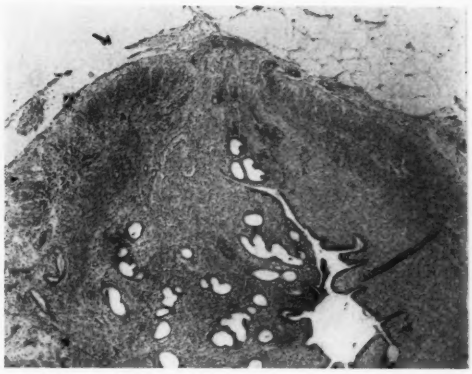

Fig. 2. Healing wound, rat uterus after 6 days (theelin). Note glandular proliferation. ×33.

response to certain internal secretions, it was believed that growth and differentiation occurring within a wound might possibly react similarly to such growth-promoting substances. It was the purpose of this investigation to study, by a quantitative method, the effect of certain endocrine substances on the healing of a soft tissue wound in a genital organ where such substances are known to exert a growth reaction. The uterus of the rat was selected as a site for such a study not only because it permitted multiple observations in a small animal but also because of the bicornuate nature of the organ which permitted the use of the uninjured horn as a control.

EXPERIMENTAL METHOD

To determine the rate of healing of incised wounds in the uterus of the normal rat the following method was used:

Healthy virgin female albino rats 6 months of age and weighing an average of 176 grams were selected. All animals were maintained on a standard diet for 1 week prior to operation. Following the operation the animals were maintained on the standard diet and kept in separate cages. The average weight change during the experiment was noted. Under sodium amytal, the uterus was exposed and a longitudinal incision approximately 1 centimeter in length was made in one horn. The edges were reapproximated with split silk using a very fine eye-needle. The same technique was employed in all cases. The stage of the estrus cycle was noted and recorded and the vascularity and size of the organ observed. The abdominal wound was closed with silk.

To determine the nature of the curve of healing in the normal untreated animals maintained on a standard diet (group 1), the animals were sacrificed at definite intervals until the sixteenth postoperative day, and the bursting strength of the wounds was determined by means of special apparatus devised. The entire uterus was excised and the stage of the estrus cycle again noted. Bursting strength of the unincised horn was noted and progress of the healing of the incision was correlated with microscopic sections of the wounds taken at various intervals (Figs. 1 and 2). In an effort to determine the effect of small amounts of theelin (group 2) on the inception of fibroplasia and early stages of differentiation, virgin female rats of similar age and weight were used. The animals were likewise maintained on a standard diet. Beginning on the day of operation each animal was given 0.5 cubic centimeter of theelin subcutaneously daily. At definite intervals these animals were sacrificed and the bursting strength of the wounds tested by the apparatus devised. Microscopic sections were obtained.

A similar study was made of the tensile strength of wounds in animals (group 3) re-

Fig. 3. Healing wound, rabbit uterus, 6 days postoperative (hysterotomy). ×22.

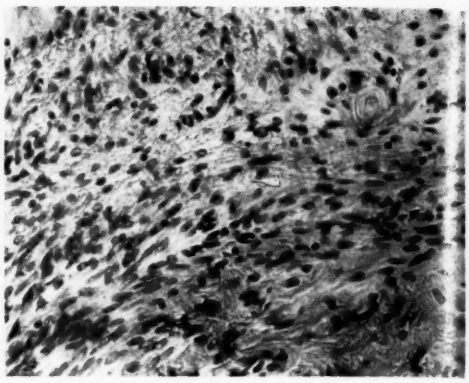

Fig. 4. Healing wound (same as Fig. 3). ×302. Note abundant cellular fibroblastic tissue.

ceiving large doses of estrogenic hormone (estradiol propionate) 0.5 milligram (4 c.c.) subcutaneously daily beginning 1 week prior to operation. In an additional group the animals received progesterone 0.5 milligram subcutaneously daily.

To determine the rate of healing of the wound in the postpartum period (group 5), incisions were made in the uterine horns of rabbits near the end of pregnancy. The fetuses and placentas were removed and the wounds (5 to 6 cm. in length) were closed with interrupted fine silk sutures. At various intervals, tensile strength studies were made and microscopic sections obtained. A few wounds in the uterus of the pregnant and nonpregnant guinea pig were studied (Fig. 7).

RESULTS

It is apparent from inspection of the curve of healing of the uterine wound of uninjected rats (group 1) maintained on a standard diet, that the healing process within a wound in this location is preceded by an interval of approximately 4 days during which the strength of the wound is at a minimum (Chart 1). Microscopically, the wound during this phase is characterized largely by exudation with exception of the endometrium which often revealed no loss of continuity after 48

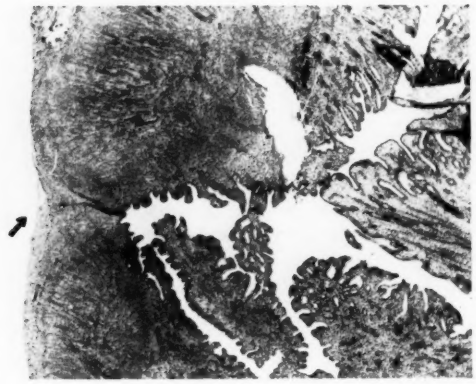

Fig. 5. Healing wound, rabbit uterus, 21 days postoperative (hysterotomy). ×22. Note presence of dense fibrous tissue.

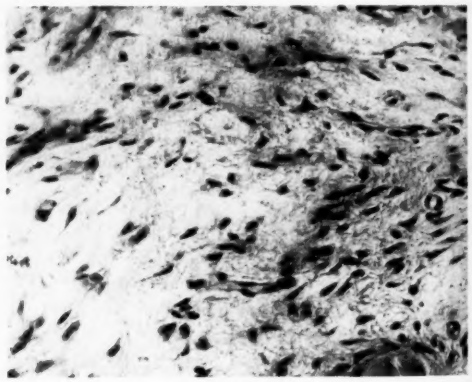

Fig. 6. Healing wound, rabbit uterus, 21 days postoperative (hysterotomy). ×302. Note dense, less cellular fibroblastic tissue.

hours. Following this initial phase there is a rapid accumulation of strength which reaches a peak in 10 to 11 days. That this increase in strength parallels the proliferation and maturation of fibroblastic tissue is apparent from study of the microscopic sections. During this period of healing studied in the rat we saw no definite smooth muscle regeneration. Once initiated the rate of growth progressively diminishes.

No appreciable deviation from the curve of response in the normal animals was observed in rats after injections of small doses of theelin (group 2). When large doses of estrogenic hormone (estradiol propionate) were injected, a delay in the accumulation of strength within the wound of the rat's uterus was noted. This effect persisted until the fourteenth day when there appeared a secondary increase in strength although never reaching the strength of the wound of the control animals (Chart 2). After injections of progesterone there appeared to be a retardation of accumulation of tensile strength of the incision. After a temporary delay, a secondary rise in strength was noted about the fifteenth day. Deciduoma formation was found in a few animals.

The process of healing of the site of incisions in the rabbit uterus (after hysterotomy) as reviewed by microscopic sections, resembles that noted in the nonpregnant rat and guinea pig (Chart 3, Figs. 3 and 4). Due perhaps to the profuse vascularity of the uterus, the exudative phase appears somewhat more marked with a rapid appearance of fibroblasts and connective tissue fibers which seem, in part, to arise from the interstitial tissue adjacent to muscle bundles. In a recent investigation, Siegel noted a similar finding in uterine incisions in the dog. The curve of tensile strength, after a period of rapid rise, is followed by a period of retarded growth and a late secondary rise. This is somewhat similar to the retarded character of healing noted in the nonpregnant rat uterus after progesterone.

Fig. 7. Wound healing, guinea pig uterus, 17 days postoperative. ×22. Marked fibroblastic reaction.

Fig. 8. Case 1. Ruptured uterine scar. Infected wound with primary section. Placenta imbedded at site of wound. ×38.

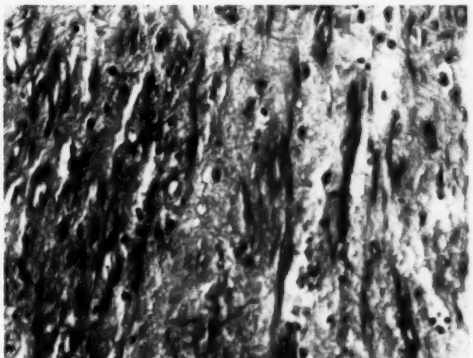

Fig. 9. Case 1. Same as Figure 8, at site of rupture. ×302. Note dense fibrous tissue with few interspersed smooth muscle fibers.

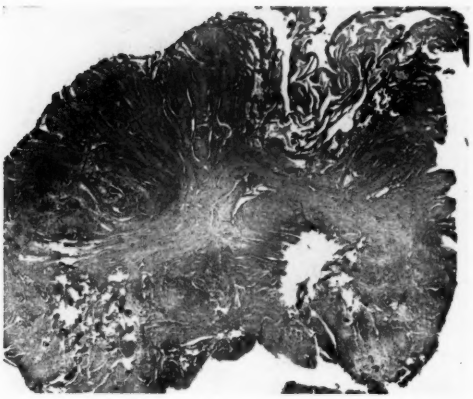

Fig. 10. Case 2. Uterine scar—two previous sections. Hysterectomy at third month of pregnancy, lower segment. Note dense connective tissue. ×7.

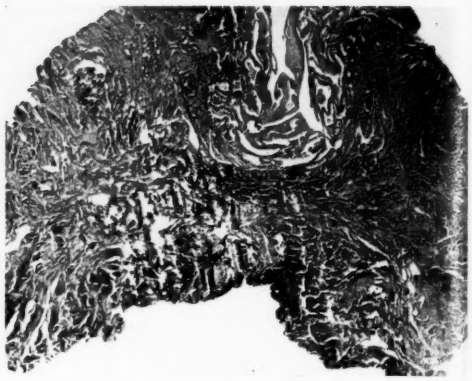

Fig. 11. Case 2. Upper uterine segment. Note presence of less fibrous tissue with infiltration of muscle fibers. ×7.

CESAREAN SECTION SCARS

The character of healing was studied in 3 postcesarean wounds of the human uterus. In all cases, microscopic sections revealed the scars to contain a preponderance of connective tissue although in some instances this was interspersed with varying amounts of smooth muscle fibers.

Case 1 represents the wound obtained at hysterectomy following rupture of the uterus at term. Pregnancy had occurred 1 year after previous cesarean section complicated by a febrile postpartum course probably due to an infected wound. The margin of the wound at the site of rupture consists almost entirely of connective tissue (Figs. 8 and 9). The placenta had been embedded beneath the site of the scar.

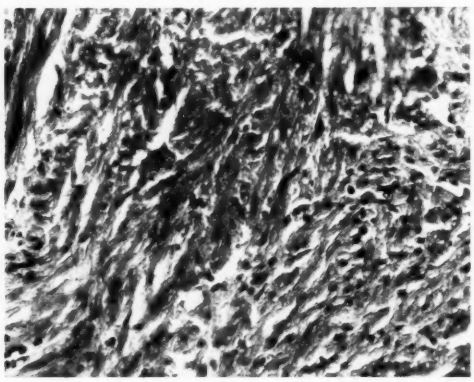

Fig. 12. Case 3. Uterine scar. ×302. Three previous sections. Hysterectomy 1 year after last cesarean. Note dense fibrous tissue with some smooth muscle.

Case 2 represents the nature of the uterine scar at 14 weeks, gestation. Longitudinal incision at previous section had involved both the upper and lower uterine segments. Microscopic study (Masson stain) reveals a greater abundance of scar tissue in portion of the wound of the lower segment. Less fibrous tissue with interspersed muscle fibers can be seen in the sections through the scar in the upper uterine segment (Figs. 10 and 11).

Case 3 represents the nature of the scar after multiple operations. Hysterectomy was done 1 year after a third cesarean section. The scar, which measured 2 to 2.5 centimeters in length, was markedly contracted. An abundance of fibrous tissue can be seen (Masson stain) with some interspersing fibers of smooth muscle (Fig. 12).

CONCLUSIONS

1. There is an increasing number of patients presenting themselves for delivery who have had a previous cesarean section. Whether or not the obstetrician elects abdominal or vaginal delivery, the possibility of rupture of the uterine wound makes important an inquiry into the nature of healing of uterine incisions.

2. Recent literature concerning rupture of cesarean incisions during a subsequent pregnancy has been reviewed. Although, in selected cases, the ability of these wounds to withstand the strain of vaginal delivery has been demonstrated, the danger of rupture is great. The character of the scars, with a consideration of factors which may interfere with normal healing, has been investigated.

3. Data are here recorded which indicate that, at least in several animal species, the initial reparative process of the uterine wound is one of fibroplasia. There is less evidence of participation of smooth muscle fibers.

4. Observations of the effect of ovarian hormones on this process and of the nature of healing of wounds of the rabbit uterus after hysterotomy have been described.

5. Examination of microscopic sections of cesarean scars indicates that healing involves mainly fibrous tissue particularly in lower segment incisions. In wounds involving the upper uterine segment smooth muscle fibers, interspersed within the connective tissue, are more abundant.

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LIGATION OF THE HEPATIC AND SPLENIC ARTERIES IN THE TREATMENT OF CIRRHOSIS OF THE LIVER

JOHN L. MADDEN, M.D., F.A.C.S., New York, New York

IN April, 1951, Rienhoff reported encouraging results in the treatment of cirrhosis of the liver complicated by ascites, hemorrhage, or both, by the ligation of the hepatic and splenic arteries. The hepatic artery was ligated distal to its gastroduodenal branch.

Stimulated by this report a similar study was undertaken, the results of which are herein presented.

CLINICAL STUDY

In the 13 month period from June, 1951, up to and including July, 1952, eight patients with cirrhosis of the liver complicated by ascites, hemorrhage, or both, were treated by ligation of the hepatic artery alone or in combination with the splenic artery (Fig. 1). The patients ranged in age from 31 to 68 years. Six were men and 2 were women. Jaundice was present in 6 patients, ascites in 7, and hemorrhage in 2. In the 2 patients with hemorrhage it was the presenting and only symptom in one and in the other it was associated with ascites.

OPERATIVE TECHNIQUE

Usually the celiac axis terminates by bifurcation into the hepatic and splenic arteries. However, in 2 (40 per cent) of a series of 5 unselected human cadaver specimens that were dissected, the hepatic artery arose from the superior mesenteric artery. This anatomic variation in the origin of the hepatic artery assumes particular surgical significance relative to ligation of the hepatic artery in the treatment of cirrhosis of the liver. Rienhoff ligated the hepatic artery distal to its gastroduodenal branch. Of the 8 patients herein reported, in 1 the hepatic propria was ligated and in the remaining 7 the hepatic artery, proximal to its gastroduodenal branch, was either ligated in continuity or divided (Fig. 1). Ligation or division of the artery at this site is easier technically and is less liable to produce necrosis of the liver.

In the isolation of the hepatic artery, the gastroduodenal artery in juxtaposition to the first portion of the duodenum is first identified as a landmark. This artery is then followed cephalad to its parent trunk, the hepatic artery. This anatomic relationship obtains whether or not the hepatic artery has its origin from the celiac axis (Fig. 3a) or from the superior mesenteric artery (Fig. 3b). In the first 6 patients operated upon, ligation in continuity of the hepatic artery was practiced. However, in 1 of these a necropsy performed 8 months postoperatively showed recannulization of the arterial lumen. Accordingly, in the last 2 patients in whom operation was performed, division and ligation of the hepatic artery were done. The varied types of operation performed are represented diagrammatically in Figure 1 and consisted of the following: combined ligation of hepatic and splenic arteries, 4 cases; ligation of hepatic artery, 2 cases; division and ligation of hepatic artery and ligation of splenic artery, 1 case; division and ligation of hepatic artery, gastroduodenal artery, and ligation of splenic artery, 1 case. Four deaths (50 per cent) resulted.

PORTAL VENOUS PRESSURE

In 5 of the 8 patients the portal venous pressure in millimeters of saline was determined. This determination was made by the insertion of a No. 18 gauge needle directly into the lumen of the portal vein rather than into one of its tributaries. In its ascent toward the liver, the portal vein passes in an oblique direction beneath the arch formed by the gastroduodenal and hepatic arteries (Fig. 2). This anatomic landmark is valuable in identifying the portal vein in a direct recording of the portal venous pressure.

From the Department of Surgery, St. Clare's Hospital, New York, N. Y.

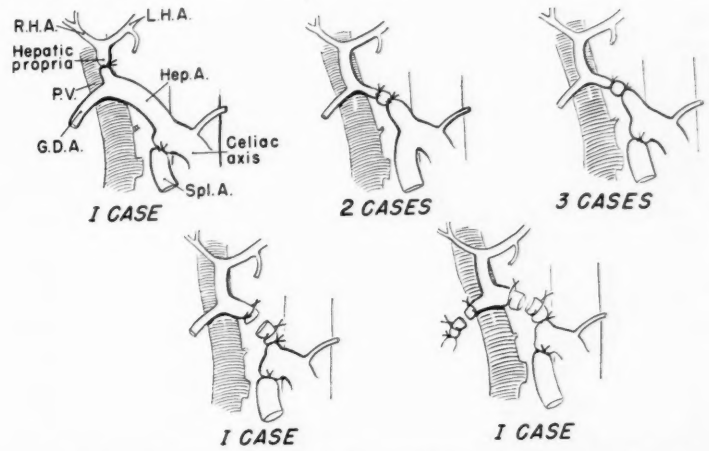

Fig. 1. Diagrammatic representation of the varied types of operation performed.

A portal hypertension was present in all of the patients in whom a record of the portal venous pressure was made. The normal venous pressure was considered as one varying between 70 and 110 millimeters of water. The pressure in the portal vein was recorded before and after the ligation of the hepatic and splenic arteries respectively. In 2 of the patients in whom a combined ligation of the hepatic and the splenic arteries was done the drop in pressure after the ligation of the splenic artery exceeded that which occurred after the ligation of the hepatic artery. In the remaining 2 the reverse was true (Table I). The initial pressures in the portal vein and the changes following the arterial ligations are depicted in Table I.

RESULTS

Of the 8 patients operated upon, 4 (50 per cent) died. In 1, acute stoppage of the heart occurred during the closure of the skin. Transthoracic manual massage of the heart was done immediately but was unsuccessful. A necropsy showed an acute thrombotic occlusion of the anterior descending branch of the left coronary artery. The cause of death in the second patient was renal insufficiency. On the fifth postoperative day oliguria occurred, terminating in complete anuria and death on the ninth postoperative day. There was no associated hyperpyrexia. On the second postoperative day a transfusion reaction occurred and conceivably was a contributory factor in the renal insufficiency. A necropsy showed extensive lower nephron nephrosis. There was no necrosis of the liver or of the spleen. The third patient died immediately postoperative from an exsanguinating intraperitoneal hemorrhage. During the operation acute and massive diffuse intraperitoneal bleeding from multiple foci suddenly occurred. In an attempt to control the hemorrhage the operative wound was packed with 5 large "leg rolls" (5 inch width). However, 3 hours postoperatively hemorrhage recurred and the patient expired. The fourth and final death was also due to hemorrhage. The presenting symptom of this patient on admission to the hospital was massive and recurrent hematemeses. There was no ascites. Initially, conservative treatment was employed. Despite the repeated use of the double balloon tube for esophageal tamponage, 3 episodes of severe hemorrhage occurred and an emergency celiotomy was done. The hepatic artery was doubly clamped, divided, and ligated. The splenic artery was ligated in continuity. The immediate postoperative condition of the patient was satisfactory. However, 40 hours postoperatively, an acute massive hematemesis occurred and the patient expired. Necrop-

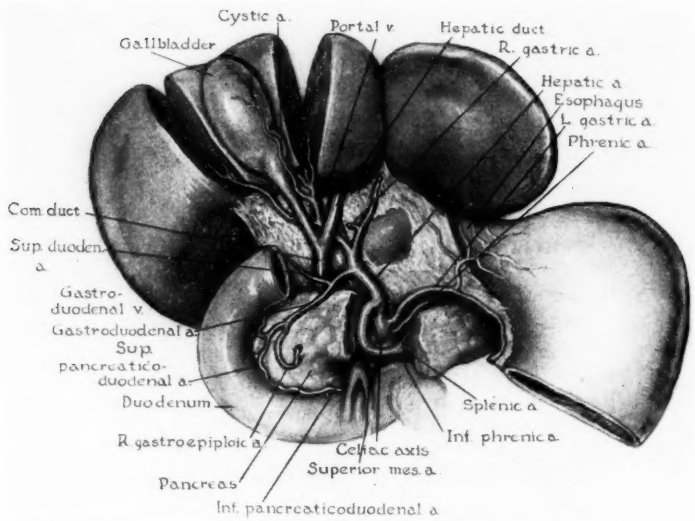

Fig. 2. Artist illustration of a cadaver dissection showing the celiac axis and its related arterial branches. The anatomic landmark for isolation of the portal vein beneath the arch formed by the gastroduodenal artery and its parent trunk, the hepatic artery, is demonstrated.

sy showed extensive varicosities of the esophagus which had ruptured. Necrosis of either the liver or the spleen was not present.

FOLLOW-UP STUDY

In the follow-up study of the 4 (50 per cent) surviving patients, 1 is living and 3 are dead. One patient died 8 months postoperatively. The original indication for operation was ascites and hematemesis. At necropsy the cause of death was exsanguinating hemorrhage secondary to rupture of esophageal varices. Approximately 8 liters of ascitic fluid were present in the peritoneal cavity. Examination of the hepatic artery at the site of ligation showed a partial recannulization of its lumen. In the second patient the cause of death was hepatic insufficiency. The indication for operation was intractable ascites. A previous history of hemorrhage was not obtained. The immediate postoperative condition of the patient was satisfactory. However, on the twenty-first postoperative day a hematemesis of approximately 500 cubic centimeters of blood occurred. Within the succeeding 6 hours there were 2 more hemorrhages, amounting to approximately 300 cubic centimeters each time. Shock was not present at any time. Three hours after the last hematemesis the patient was comatose and expired within 8 hours. The third patient died 4 months postoperatively. The indication for operation was intractable ascites of 7 months' duration. Abdominal paracenteses were required at 8 day intervals, and each time 18 to 20 liters of ascitic fluid was removed. Four months prior to operation a Crosby-Cooney button was inserted without relief. Immediately prior to ligation of the hepatic and splenic arteries, the patient was extremely ill and was the worst risk of anyone in the series. The operation was performed as a last resort, inasmuch as the patient continued to get progressively worse despite a prolonged and adequate medical regimen. The immediate postoperative condition was surprisingly good and the condition of the patient 8 weeks postoperatively was classified as excellent. However, 3 months postoperatively there was a gradual reaccumulation of ascitic fluid. During the succeeding month an abdominal paracentesis was done at intervals of 10 days, and

each time approximately 14 liters of ascitic fluid were removed. However, 3 days after the last paracentesis there was a sudden attack of abdominal pain associated with recurrent hematemeses. These symptoms were persistent and 2 days after their onset the patient died. A necropsy showed a generalized peritonitis and rupture of esophageal varices. The peritonitis was presumed secondary to a transgression of the lumen of the bowel at the time of the last paracentesis.

The condition of the 1 surviving patient, 1 months postoperative, is poor. The primary indication for the operation was ascites. Eight months after operation the patient was readmitted to the hospital because of gastrointestinal bleeding and recurrent ascites. Since this time repeated admissions to the hospital because of the same symptoms have been necessary.

COMMENT

Before commenting on the effects of ligation of the hepatic and splenic arteries in the treatment of cirrhosis of the liver complicated by hemorrhage or ascites, or both, it is believed important to stress that the patients subjected to this operation were extremely poor risks. On admission to the hospital, 6 of the 8 patients were jaundiced, and none was a suitable candidate for a portacaval anastomosis. In fact, because of the unsatisfactory results previously obtained, the use of portacaval shunts in the treatment of patients with cirrhosis of the liver complicated by ascites is neither practiced nor recommended.

The main indication for ligation of the hepatic artery was the failure of the patient to respond to a prolonged and adequate medical regimen and, in a surgical sense, the lack of anything else to offer the patient. Two patients were treated previously by the insertion of the Crosby-Cooney button. There was a temporary improvement in one but in the other there was none.

Following the ligation of the hepatic artery, a constant observation has been the occurrence of a persistent and deep violaceous hue to the mucous membranes of the lips and to areas of cutaneous telangiectasia if such are present. No explanation for this phenomenon is offered.

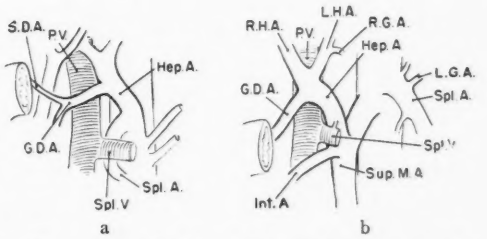

Fig. 3. Sites of origin of the hepatic artery. a, Celiac axis. b, Superior mesenteric artery.

In only 1 patient was hemorrhage the primary and only indication for operation. The hemorrhage was acute, massive, and recurrent, secondary to ruptured varicosities of the esophagus. In the other, hemorrhage and ascites were coexistent symptoms. In neither patient was ligation of the hepatic and splenic arteries effective, either in the control of the acute hemorrhage or as a prophylaxis for recurrent hemorrhage.

Three patients in whom the indication for operation was intractable ascites bled for the first time from the gastrointestinal tract after the operation was done. In 1, moderate hematemesis occurred 3 weeks postoperatively. The hemorrhage recurred twice within a period of 6 hours and was associated with hepatic insufficiency, coma, and death. In another, melena occurred on the fifth postoperative day and recurred daily for a period of 4 days. The blood loss was moderate and required a total blood replacement of 2,000

TABLE I.—PORTAL VENOUS PRESSURES

	Direct recording in mm. of isotonic saline				
	1	2	3	4	5
Initial pressure	399	482	425	410	321
Ligation of hepatic artery proximal to gastroduodenal artery	375 (24)	460 (22)	412 (13)	398 (12)	303 (18)
Combined ligation of hepatic and splenic arteries	344 (31)	421 (39)	405 (7)	—	298 (5)
Total decrease in portal venous pressure	55	61	20	12	23

Numerals in parentheses indicate the decrease in the portal venous pressure after ligation of the hepatic and splenic arteries respectively.

cubic centimeters to correct the deficit. This patient expired 4 months after operation. The cause of death was generalized peritonitis. During the 2 days prior to death massive and recurrent hematemeses occurred. The third patient, and the only survivor, bled for the first time 8 months after operation. During the succeeding 7 months up to the present time recurrent bouts of hemorrhage have occurred.

In an analysis of the immediate mortality statistics, one may note that in 3 of the 4 patients who died the cause of death was not directly related to the ligation of the hepatic and splenic arteries. The 1 death that was conceivably the direct result of the operation was caused by renal insufficiency. An additional contributory factor to the death of this patient was a transfusion reaction which occurred on the second postoperative day.

Of the 4 deaths, 2 patients survived for a sufficient period to evaluate the effect of the ligation of the hepatic and splenic arteries on the liver and spleen respectively. At necropsy there was no evidence of necrosis of the liver or spleen. In the 4 patients who survived the operation there was no clinical evidence of liver necrosis. Three of these 4 patients subsequently died, 8 months, 4 months, and 3 weeks postoperatively, respectively. At necropsy there was no evidence of necrosis of either the liver or the spleen.

Following the results obtained in the 8 patients operated upon, the efficacy of ligation of the hepatic and splenic arteries in the treatment of cirrhosis of the liver is seriously questioned. The fundamental concept of the operation, based on the perfusion studies of Herrick and, more recently, Dock, is not believed a sound one either anatomically or physiologically. The results obtained after ligation of the hepatic artery in the patients herein reported do not warrant its continued usage.

CONCLUSIONS

In the treatment of cirrhosis of the liver ligation of the hepatic artery may be performed immediately distal or proximal to its gastroduodenal branch without causing liver necrosis.

Similarly the splenic artery may be ligated without causing necrosis of the spleen.

In this series ligation of the hepatic artery has not proved efficacious either in the control of acute massive hemorrhage or as a prophylaxis for recurrent hemorrhage from rupture of esophageal varices.

The efficacy of ligation of the hepatic and splenic arteries in the treatment of cirrhosis of the liver complicated by ascites, hemorrhage, or both, is seriously questioned. The continued use of the operation is not recommended.

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CONTRACTURES OF THE ILIOTIBIAL BAND

EINER W. JOHNSON, JR., M.D.,
Rochester, Minnesota

EVEN though all of the contractures of the iliotibial band do not arise as a consequence of acute anterior poliomyelitis, it is nevertheless this group of contractures of the iliotibial band which have been of considerable interest in the past. Ormley and Allen have stated that the deformities arising from anterior poliomyelitis may be grouped into three main categories. These are the deformities which are due to muscular imbalance, the deformities due to or caused by stretch paralysis of muscles, and the deformities which are caused by fascial contractures. It is this last group of deformities with which I am most interested in discussing contractures of the iliotibial band and the deformity which arises as a consequence of this contracture.

Yount, in 1926, wrote an article which is still widely quoted. He thoroughly discussed the anatomy of the iliotibial band and the relationship of this anatomy to the deformity caused by contracture of the iliotibial band. In his article, Yount made three main points.

1. The gluteus maximus and tensor fasciae latae muscles are the most important factors in the formation of hip flexion deformity. Yount, at this time, made the point that it is not the iliotibial band and its attached lateral intermuscular septum which is of importance so much as it is the muscles which are inserted into this band and septum.

2. The knock knee deformity which accompanies these hip flexion deformities is caused by the continuation of the iliotibial band distal to the knee joint itself.

3. The biceps femoris muscle, the short head of which arises from the iliotibial band, is most important in the causation of external rotation deformities of the leg on the thigh.

Ober, writing in 1936 and again in 1941, stressed the importance of the iliotibial band and contraction of this band as a causative factor in lumbosacral, sacroiliac, and sciatic pain. It was Ober's idea that shortening of the iliotibial band produced unusual stress on the lumbosacral and sacroiliac joints, thus causing pain in these areas. The obliquity of the pelvis so created also compresses the sciatic nerve near the pyriformis muscles thus producing sciatica. Ober, in his first article, reported 42 cases of lumbosacral or sacroiliac pain associated with sciatica, and stated that in 23 of these cases the pain had been relieved by the fasciotomy which now bears his name. In 1941, he had expanded his series to 86 cases, but at this time presented no overall statistics as to curative rate. Mennell, writing in 1944, discussed the symptoms of contractures of the iliotibial band and listed the methods of nonoperative treatment. These consisted primarily of stretching and postural exercises. However, it remained for Irwin, in 1949, to make the best analysis of the deforming properties of the iliotibial band and to give a good discussion of the treatment of these deformities.

At this juncture, it might be wise to consider why fascia is involved in anterior poliomyelitis. Almost all of the pathologic teaching in medical schools and textbooks to date has to do with the involvement of the central nervous system by the virus of anterior poliomyelitis.

Carey, Massopust, Zeit, and Haushalter, in 1944, demonstrated that the motor nerve endings in the muscles were involved by the virus of poliomyelitis. Pohl strongly believed that the invasion of the body with anterior poliomyelitis leaves no particular tissue untouched. By reason of the pain, tenderness, and, later, the inelasticity and thickening which develop in the skin, Pohl expressed the opinion that the skin is involved in poliomyelitis. The sudden and relentless atrophy of the subcutaneous fat following onset of the acute phase of polio-

From the Section of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota.

Fig. 1. Side view of contracture of the iliotibial band showing flexion contracture of the hip and knee on the side nearest the camera with equinovarus deformity of the foot.

myelitis was evidence to Pohl that this section of the body is involved. The tenderness of the muscles to pressure and the shortening of the plantar fascia as well as other fascial bands of the body also demonstrated to Pohl that these elements were not spared. Bell and Clawson said that there is probably no involvement other than that which occurs at the anterior horn cells and the central nervous system in general. They have noted myositis as well as myocarditis in several cases of fatal poliomyelitis. However, analyses of other groups of fatal cases due to other virus diseases have shown an even higher incidence of myositis and myocarditis. Therefore, these authors concluded that these two findings are probably of no significance. Irwin has the most sensible idea of the involvement of the fascia by poliomyelitis. It was his opinion that it is not the fascia which is involved but the muscles which are inserted into it. These exert a pull and, therefore, produce the eventual shortening of the fascial layers.

Fig. 2. Front view of the same patient as in Figure 1, showing valgus of the leg on the thigh, and pelvic obliquity.

The complete syndrome often referred to as contracture of the iliotibial band is composed of eight main categories. These are as follows: (1) flexion, abduction, and external rotation of the hip joint; (2) genu valgum and flexion contracture of the knee joint; (3) leg length discrepancy; (4) external torsion of the tibia on the femur with or without subluxation of the knee; (5) secondary equinovarus deformity of the foot; (6) external torsion of the femur; (7) pelvic obliquity; (8) increased lumbar lordosis.

It is obvious from the consideration of the multiplicity of the deformity as outlined that to produce such a deformity of the iliotibial band there must be considerable ramification in its anatomy. This is the case. The iliotibial band, or rather the fascia on the lateral aspect of the thigh, commonly referred to as the iliotibial band, has numerous attachments. Proximally, it is attached to the coccyx, sacrum, the crest of the ilium, anteriorly over Poupart's ligament, to the ramus and the tuberosity of the ischium, and to the lower part of the sacrosciatic ligament. Distally, the same expanse of fascia is attached to the lateral tuberosity of the tibia, to the head of the fibula, to the external condyle of the femur, and into the entire course of the lateral intermuscular septum existing between the hamstring muscles and the vastus lateralis muscle. Therefore, it is secondarily inserted into the linea aspera since the lateral intermuscular septum is attached to the linea aspera of the femur. The iliotibial band itself lies in a plane which is anterior and lateral to the main axis of the hip joint and posterior and lateral to the midpoint of the knee joint.

With these anatomic points in mind, it is therefore possible to correlate the complete deformity with the anatomy of the iliotibial band. The flexion and abduction deformity of the hip occurs because of the position of the iliotibial band in relationship to the hip joint. Since this band lies anteriorly and laterally to

the hip joint, it is reasonable to assume that in shortening of the band the hip joint will be drawn into flexion and into some abduction. With this deformity taking place, the patient assumes the position of comfort which, therefore, brings the femur into external rotation, hence the flexion, abduction, and external rotation deformity of the hip joint. The genu valgum and flexion contracture of the knee are produced by the position of the iliotibial band in relation to the knee joint. Since it lies posteriorly and laterally and is attached to the tuberosity of the tibia as well as in the head of the fibula, this force then produces a backward pull on the leg in relation to the femur, hence the flexion deformity. The genu valgum is produced by drawing the tibia laterally in relation to the femur. The disparity in leg length existing in this deformity may be due to one of two causes. The obvious shortening of the involved extremity may well result from the withdrawal of the stimulation to the epiphysis produced by normal contractions of the muscles of that leg. This, therefore, reduces the epiphysial growth and hence produces a shortening of the involved side. One other explanation of this disparity in leg length might well be the fact that the iliotibial band by reason of its insertion into the linea aspera through the lateral intermuscular septum produces a very direct effect upon the proximal and distal femoral epiphysis as well as on the proximal tibial epiphysis. It has been conjectured that this tight fascial band might well produce enough compressive force upon these epiphyses to limit their growth. As was mentioned earlier, the short head of the biceps femoris is attached to the iliotibial band, and it is this muscle which has been implicated as one of the factors causing the external torsion of the tibia. This external torsion of the tibia, if allowed to proceed to its ultimate end, may well produce subluxation of the knee joint.

The secondary equinovarus deformity of the foot which has been listed as one of the components of this deformity is actually not a true change occurring with this deformity. It is actually a secondary deformity which results because of the physician's attempt to place a leg so deformed in a long leg brace with a nonrotating pelvic band. The patient's attempt to bring the foot into weight-bearing alignment after being placed in this brace results in the equinovarus deformity of the foot since it is only with this positioning of the foot in the face of an external rotation deformity of the tibia that the patient can put his foot in a weight-bearing position. Hence, this is truly a secondary deformity and not one commonly allied with contracture of the iliotibial band. The external torsion of the femur is produced by long standing contractures of the iliotibial band since its insertion along the entire length of the femur therefore allows it to attain great purchase on the shaft of this bone. The result of this purchase is to produce a gradual torsion in the femur with its main component externally.

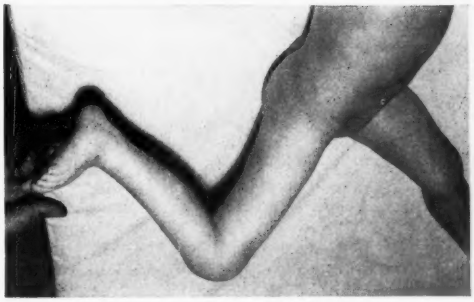

Fig. 3. Positive result of Ober's test on patient shown in Figures 1 and 2.

The last two elements of this deformity, namely, the pelvic obliquity and the increased lumbar lordosis, are not difficult to understand when one considers that the gluteus maximus and tensor fasciae latae muscles are inserted into the iliotibial band. This insertion occurs just distal to the greater trochanter and thus produces a relative shortening of the distance between the greater trochanter and the lateral pelvic wall. Because of this relative shortening of the distance between the greater trochanter and the lateral wall of the pelvis, the leg is obviously held in abduction. To bring the leg into proper weight-bearing line, it is necessary for the patient to tip the pelvis toward the side of the deformity, thus producing a pelvic obliquity. To compensate for this obliquity, there is produced a secondary lumbar scoliosis. The natural component of the

Fig. 4.

Fig. 5.

Fig. 4. Postoperative view showing correction of deformity about the knee and hip which were dislocated.

Fig. 6.

Fig. 5. Anterior view of patient. The discrepancy in the length of the legs is still apparent but there is some correction of the valgus deformity of the leg on the thigh.

Fig. 6. Postoperative result with eradication of the positive Ober's sign.

flexion deformity is to produce a lumbar lordosis. Thus, by an analysis of the various anatomic attachments of the iliotibial band, it is possible to demonstrate and to visualize how these attachments influence the development of the complete syndrome (Figs. 1, 2, and 3).

The recognition of this deformity is primarily one of being aware of its presence. The Ober test has been very helpful in impressing these deformities upon our minds. This test is performed by having the patient lie on his side and draw the inferior leg well upon the abdomen, thus obliterating the lumbar lordosis. With the examiner standing behind the patient, the uppermost leg is grasped and drawn, with the knee flexed, into a position in which the thigh is in the long axis of the leg. In this position, if the iliotibial band is taut, the knee cannot be depressed to touch the table. The result of the test is considered normal if the knee can be brought inferiorly far enough to touch the table. This maneuver along with the recognition of the remainder of the deformities already listed will help one greatly in recognizing the true deformity.

As to treatment of this deformity, some general points might well be brought out. The most obvious fact is that the best treatment is prevention. Wherever practical, it is wise to put each extremity that is involved in poliomyelitis through a full range of passive, if not active, motion each day. However, once the deformity is well developed, there is very little other than surgical means which can be used to treat it. There are some advocates of stretching of the iliotibial band, but it has been our experience at the Mayo Clinic that this is a tedious process which is not altogether effective. Our feeling is that the ultimate treatment should be surgical to attain as rapid and as complete resolution of the deformity as possible. As far as poliomyelitis is concerned, this is one form of surgical treatment which can well be taken care of prior to the lapse of the usual 2 year waiting period following the acute onset. Since it is the nature of this deformity to increase in severity the longer it exists, it has been recommended that surgical attack on the problem be undertaken as soon as the deformity is recognized.

The Yount fasciotomy has been used extensively in the surgical treatment of this disability. It has been our feeling at the clinic that the Soutter fasciotomy as well as the Ober fasciotomy is of secondary importance and of less genuine use to the surgeon. Nevertheless, we occasionally see a case in which the flexion deformity of the hip is still not corrected after a Yount fasciotomy, and in such a case it has been our policy also to perform a Soutter fasciotomy. As one might imagine, in the cases in which both fasciotomies were indicated, the deformities were severe, and, hence, the results were not as good

as those expected in cases in which the deformities are less severe.

Irwin, in his excellent article, has outlined a form of treatment which has sound basic principles. Following a Yount fasciotomy, Irwin places the normal leg in a long leg cast with the knee straight and the ankle at 90 degrees. In this cast, he incorporates a Kirschner wire with its traction pull so adjusted that the healthy leg is fixed solidly in the plaster. This long leg cast is then incorporated in the body piece of a double spica cast, thereby fixing the well leg and the body as one controllable unit. While these two sections are being applied to the cast, the involved leg is held in abduction and flexion so as to level the pelvis and obliterate the lumbar lordosis. Following the application of the cast to the sound leg along with the transfixing supracondylar wire and traction bow, and the application of the body portion of the jacket, the involved leg is incorporated to this cast as a final step. Therefore, the end result of these three steps is a double spica cast with fixed traction on the healthy leg. Thereafter, at intervals of 4 to 6 days, the involved leg is wedged to meet the normal leg in such a manner as to remove the flexion and abduction deformity, and in doing so it greatly stretches the iliotibial band. This wedge cast has been used in only 1 of the 28 cases of this type of contracture in which the patients have been treated surgically at the clinic.

It was the feeling of one of my colleagues (Janes) that the use of a wedge cast, as outlined previously, is not necessary to maintain postoperative correction of the deformity. It has been our policy to follow the operation with institution of Buck's extension to each leg along with nonrotating foot splints. This type of traction, maintained by using 4 to 6 pounds (1.8 to 2.7 kgm.) of weight, depending upon the size of the child, has been used for 3 weeks in each of our other 27 cases. To date, our results have completely justified this simplification of Irwin's therapeutic procedure. A reporting of this modification of Irwin's treatment is, therefore, the justification for this publication (Figs. 4, 5, 6, and 7).

To now, operations for this deformity have been performed on 28 patients at the clinic Not all of these deformities were due to poliomyelitis. In 1 case, the patient had myelodysplasia and the deformity developed as a result of constant rest in bed. In another case, the patient had traumatic paraplegia and the deformity also developed because of confinement in bed. In the third case the deformity was caused by myoblastoma of the lateral aspect of the distal portion of the thigh, and it seemed to be caused by the extreme protective attitude the child developed because of severe tenderness of the tumor. This last case was the only one of our series in which the wedge cast method outlined by Irwin was used. In all of these cases, the results have been satisfactory to the clinician, to the patient, and to his or her relatives. It is difficult to tabulate accurately the degree of deformity in the correction obtained, since this involves exhaustive record keeping. However, I believe that our results have been satisfactory.

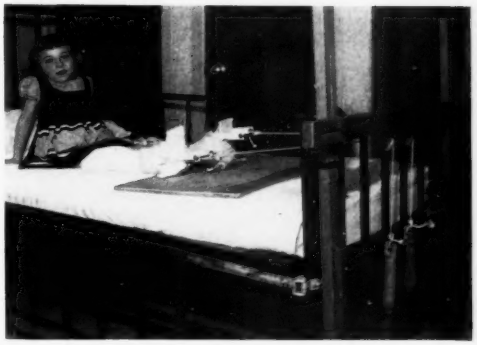

Fig. 7. Postoperative care which all but 1 of our patients have received. The cast on the right extremity was used because a tendon transplant was also done at the time of the Yount fasciotomy. The nonrotating apparatus on each splint should be noted.

As to the time of treatment, it was well brought out in our series that the longer the deformity has existed, the greater will be the degree of the deformity, and also that the greater will be the difficulty in attaining a good result following operation. It has been brought home to me time and time again that the earlier the operation is performed the better will be the result.

SUMMARY

Contractures of the iliotibial band are common following acute poliomyelitis. The com-

plete deformity consists of flexion, abduction, and external rotation of the hip joint, genu valgum and flexion contracture of the knee joint, discrepancy in the length of the legs, external torsion of the tibia on the femur with or without subluxation of the knee, secondary equinovarus deformity of the foot, external torsion of the femur, pelvic obliquity, and increased lumbar lordosis. This is one deformity which follows poliomyelitis and can be treated surgically as soon as recognized. The deformity can be treated by a modification of the wedged cast method advocated by Irwin. This modification consists of the use of Buck's extension for 3 weeks after operation. To date, the results have thoroughly justified this simplification of Irwin's method.

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THE PRODUCTION BY LIQUID NITROGEN OF ACUTE CLOSED CEREBRAL LESIONS

RAYMOND A. CLASEN, M.D., DAVID V. L. BROWN, Captain, M.C., SEYMOUR LEAVITT, B.S., and GEORGE M. HASS, M.D., Chicago, Illinois

ACUTE expanding closed cerebral lesions in patients present many problems, related principally to pathogenesis of symptoms and choice of treatment. Much conflict of opinion about these matters has arisen because they cannot be studied in complicated human cases in a quantitative way. A method for the experimental production of acute closed cerebral lesions in rabbits made it possible to conduct some quantitative studies (2). The lesions were produced by freezing parts of the cerebrum by applying an instrument cooled by expanding carbon dioxide against the external surface of the calvarium. The method was refined so that discrete cerebral lesions of desired volume could be reproduced in successive animals without interrupting the continuity of the calvarium or introducing variables incidental to mechanical trauma (3). After standardization of the procedure it was used to study the relations between the volume per cent of cerebral damage and clinical manifestations, not only in untreated animals but also in animals treated with hypertonic intravenous glucose or surgical decompression (4). Furthermore, the effects of the production of progressive increments of cerebral damage by multiple successive lesions spaced at various intervals of time were investigated (5). The data obtained from these studies indicated that application of the methods to larger animals and their extension to include additional quantitative measurements would be justified as a step toward a better understanding of the complex problem of acute cerebral injury.

From the Rush Departments of Pathology and Ophthalmology, Presbyterian Hospital, Chicago, Illinois, in affiliation with the University of Illinois.

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METHOD AND PROCEDURE

Production of closed cerebral lesions. Mongrel dogs weighing 9 to 18 kilograms were used. The experimental animal was anesthetized with sodium pentobarbital and fastened in a prone position to an animal operating table. The head was rigidly fixed by means of mandibulomaxillary clamps to a steel frame with the naso-occipital axis of the skull parallel to and slightly above the long vertebral axis. The hair was clipped from the scalp. A midsagittal double cross bow frontoparietal and parieto-occipital incision was made. The scalp was reflected laterally and downward to expose the superior convexity of one or both parietal bones. The temporomandibular muscles were then dissected away from their insertions in the galea aponeurotica and periosteum. Electrocoagulation was used to assure hemostasis. Thus the concave-convex external surface of one or both parietotemporal areas of the skull was exposed.

A special container for holding isopentane and liquid nitrogen was then sealed to the periosteum of the skull overlying the portion of the brain in which the lesion was to be produced. A rim of aquarium cement was used to insure a proper seal. The container may be described briefly as follows: It consisted of 2 concentric brass cylinders. The inner cylinder, open at both ends, was 10 centimeters in length and 10 millimeters in diameter. The external cylinder, open at one end, was tapered conically at the other end where it was welded to the distal rim of the inner cylinder. The external cylinder was 10 centimeters in length and 65 millimeters in maximum diameter. This container, while the distal end was being cemented to the external surface of the calvarium, was transfixed with adjustable clamps to the head-holding steel frame. Any slight motion of the skull moved the cylinder.

The actual production of the cerebral lesion by freezing was done in the following way: Isopentane previously chilled with liquid nitrogen was poured into the open proximal end of the inner cylinder until it was about one-half full. The distal end of the confined column of isopentane was, therefore, in direct contact with the periosteum or bone of the skull. Liquid nitrogen was then poured into the external cylinder and maintained there in sufficient volume to surround that part of the internal cylinder containing isopentane. The rapidly chilled instrument was held in position for times varying from 2 to 10 minutes. It was then evacuated, warmed with normal saline, and disengaged from the skull. Lesions of desired controlled dimensions were thus produced in frontal, parietal, and occipital areas of the superior convexity of one or both cerebral hemispheres in a large series of dogs.

Measurements of cerebrospinal fluid pressures. After reflecting the scalp from the calvarium and before production of the cerebral lesion by freezing, an ordinary spinal lumbar puncture needle was inserted through the intact cervical muscles and the atlanto-occipital membrane into the cisterna magna. This needle was connected by a short piece of plastic tubing to a strain gauge or pressure transducer. Care was taken to assure a continuous column of liquid from the subarachnoid space to the chamber of the transducer. This volume of liquid remained essentially constant throughout the experiment and there was no loss of cerebrospinal fluid. The transducer in turn was connected by electric wiring to an electronic current amplifier or pressure analyzer which activated one channel of a double channel direct inking oscillograph. Direct continuous or interrupted tracings were made on rolls of standard recording graph paper.

Measurement of pressures within the aorta and inferior vena cava. A polyethylene catheter was passed into the femoral artery so that its distal end was in the lower abdominal aorta. The proximal end of the catheter was connected to a strain gauge or pressure transducer and a continuous fluid junction was established. The pressure recording was carried out through a second pressure analyzer which drove the second pen of the double channel direct inking oscillograph. Simultaneous continuous tracings of intra-aortic blood pressure and cisternal spinal fluid pressure were thus made available.

The blood pressure within the inferior vena cava was recorded by inserting the distal end of a polyethylene catheter into the vena cava through the femoral vein. The proximal end of the catheter was connected to a water manometer provided with a scale. Readings were made visually and recorded in absolute values at desired intervals of time.

Ophthalmoscopic studies. After the animal had been anesthetized, the pupils were dilated by instilling scopolamine or homatropine and paredrine into each conjunctival sac. Four sutures were placed in the conjunctiva of each eye to control motion and fixation of the eye in desired positions. The cornea of each eye was moistened with methyl cellulose (1 per cent) and specially made corneal contact lenses were placed in position. The optic fundi were then studied at intervals by use of the Gullstrand binocular ophthalmoscope and a hand electric ophthalmoscope. Under these conditions the cornea remained clear and changes in the blood vessels and optic discs were observed for as long as 10 hours covering the period before, during, and after the production of cerebral lesions by freezing. In several selected experiments photographs of the fundi were taken at intervals with a fundoscopic camera.

Postmortem studies. At the conclusion of each experiment, the animal, if still living, was sacrificed with an overdose of sodium pentobarbital. The spinal puncture needle was disengaged from the pressure transducer and connected to a syringe containing india ink. A small quantity of india ink was injected into the spinal needle.

The calvarium was then removed. The dura was reflected and a record was made of the gross appearance of each lesion produced by freezing. Special attention was directed to the presence or absence of subarachnoid or subdural hemorrhage over and at a distance from each lesion. The frontal lobes were then retracted from the base of the skull and each optic nerve transected at the optic chiasm.

The brain was then retracted further and removed from the skull after transecting the spinal cord at the level of the first cervical segment. The cisterna magna was examined and the location of the india ink which had been injected through the spinal needle was noted. The brain was fixed in formalin (10 per cent).

Both eyes together with the optic nerves were dissected out and fixed in Mueller's solution. A complete examination of the thoracic and abdominal viscera was then made.

Representative blocks of tissue from the brain, cerebral lesions, optic nerves, and eyes were embedded in celloidin or paraffin. Sections for microscopic study were stained routinely with hematoxylin and eosin. Several special neurological stains were used to bring out particular details, when indicated.

Measurement of the volume per cent of cerebral damage. After fixation of the brain in formalin, it was first weighed in air and then while immersed in distilled water. The volume of the brain was calculated from these weights. A template of the external surface of each cerebral lesion was prepared and transferred to graph paper having transverse and perpendicular lines at intervals of 1 millimeter. The surface area of the lesion was then determined by summing the number of squares circumscribed by the margin of the template. Coronal sections of the brain were made by a series of transverse incisions spaced at intervals of about 5 millimeters. The average depth of each lesion was measured. The volume of each lesion was estimated as the product of the values for the surface area and average depth. The volume per cent of cerebral damage was the ratio of the volume of cerebral damage to the volume of the brain. One observer made all measurements. A permanent photographic record of the external surface and cross sectional areas of each lesion was made.

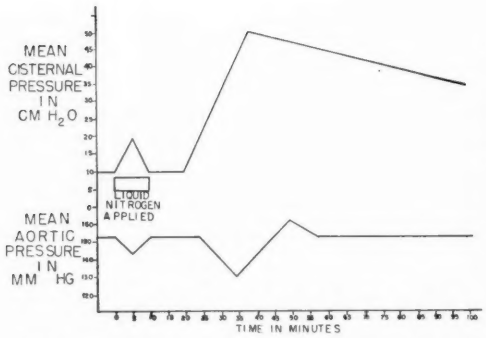
RESULTS

Production of lesions of brain. Four factors were of importance in obtaining cerebral lesions of reproducible desired dimensions and location.

The first of these was standardization of contact of the cooling fluid with a desired area of the external surface of the calvarium. In early experiments, several sizes and shapes of containers with open and closed ends were used and liquid nitrogen alone was used as the cooling fluid. Difficulty was encountered in obtaining uniform approximation of closed ends of metal tubes to the calvarium. Also, we were unable to maintain a uniform liquid seal between the closed end of the container and the calvarium. When the closed containers were replaced by cylindrical tubes with open ends, the principal difficulty was loosening of sealing materials placed at the junction of the rim of the tube and the calvarium. This was due to the variable expansion coefficients of the metal tube, the tissues, and materials used for maintaining a seal. Leakage of liquid nitrogen from the cylinder occurred at the site of the seal. The use of aquarium cement solved this problem. It was found, however, that when liquid nitrogen was poured into the cylinder, the vigorous bubbling disturbed continuity of contact of the liquid nitrogen with the calvarium. This was overcome by use of a double cylinder, by pouring isopentane in the inner cylinder and cooling the isopentane by pouring liquid nitrogen into the surrounding external cylinder or jacket. This final method worked very well except over these areas of the calvarium where irregularity in contour was unduly great. These areas were avoided in the production of most lesions.

The second factor of importance in governing reproducibility of lesions was the variable thickness of the calvarium from place to place in the same animal or in some particular location among different animals. This factor could not be entirely eliminated but the choice of mongrel dogs of about the same size reduced its importance. This did not eliminate the natural variations in the thickness of the calvarium from place to place in the same dog. This was not very important, however, in the present experiments, in which most lesions were made beneath areas of the skull where variation in thickness amounted to no more than 1 to 2 millimeters. The maximum depth of penetration of the lethal effects of cooling was about 20 millimeters.

The third factor of importance in obtaining reproducible lesions was the area of contact



Graph 1. The average relations between the cisternal pressure and the mean of the diastolic and systolic intra-aortic blood pressures before, during, and after the production of acute closed cerebral lesions produced by liquid nitrogen.

between the cooling liquid and the calvarium. In general, the surface area of the lesion in the cerebrum was proportional to this area of contact, provided the duration of contact was held constant. We chose to work with a standard area of contact in most experiments. It is clear, however, that lesions with very large or very small surface areas could easily have been produced by enlarging or diminishing the area of contact between the cooling fluid and the calvarium.

Duration of contact between the cooling fluid and the calvarium was another factor which governed the reproducibility of lesions. All other things being equal, the longer the duration of contact in the time interval from 1 to 10 minutes, the greater the depth and breadth of the lesion in the cerebrum. Superficial cortical lesions with about the same surface area as the diameter of the cooling cylinder were produced in about 2 minutes. Deep lesions extending down to the walls of the lateral ventricles with surface areas about three times the diameter of the cooling cylinder were produced in 8 to 10 minutes. There was no good evidence that prolongation of the cooling beyond 10 to 15 minutes increased the dimensions of lesions to a significant degree.

With proper attention to the regulation of these factors, lesions of approximately the same desired dimensions and location could be reproduced in the same animal or in successive animals.

Measurement of pressure. The technique for the measurement of cisternal pressures was satisfactory in most cases. There were two principal sources of error. One was due to partial or complete obstruction of the lumen of the spinal puncture needle by blood clot or tissue. At times, despite this occlusion, tracings of pressure change due to arterial pulsation and respiratory excursion were obtained. This was doubtless due to the extreme sensitivity of the recording system. Another source of error was due to location of the tip of the spinal puncture needle at some point outside of the cisterna magna. For this reason we found it necessary to inject india ink into the spinal needle at the conclusion of each experiment. If the needle was in an undesired position, the distribution of the india ink as visualized on removal of the brain clearly indicated this source of error.

It is to be emphasized that we were dealing here with measurements of cisternal pressures. These pressures were not necessarily a true indication of the intracranial pressure anywhere except in the cisterna magna. However, our efforts, thus far, to obtain accurate supratentorial pressures have been unsuccessful.

The average curve of the cisternal pressure of 26 animals before, during, and after the production of cerebral lesions of various dimensions is shown in Graph 1. This shows an initial transient and a delayed prolonged elevation of cisternal pressure. The initial elevation corresponded in time with the period of induction of freezing the brain. We have attributed this to the expansion of the cerebral tissue during freezing though this may not be the proper explanation. In any event after the cerebral tissue was frozen solid, the cisternal pressure by some compensatory mechanism returned to a normal level for several minutes before undergoing a secondary rather sharp constant rise to a maximum level. The period preceding this secondary rise was correlated in time with the period during which the brain remained solidly frozen. As the frozen brain thawed, the lesion developed to completion over a period of several minutes. The development of the lesion with the accompanying vasodilatation, perivascular hem-

orrhage, necrosis, and edema coincided in time with the delayed secondary prolonged elevation of cisternal pressure. In the hours after the full development of the lesion, there was usually a progressive slight fall in the cisternal pressure.

It is to be noted that the average maximum cisternal pressure in this series of animals was about 50 centimeters of water. The range of elevation of pressure in this series was 5 to 120 centimeters of water. This was a very useful range for experimental purposes because it spans rather closely the range found in most human disease in which elevation of intracranial pressure is encountered.

The second curve on Graph 1 illustrates the average of the mean of the systolic and diastolic intra-aortic blood pressures in the 26 animals. In general, the behavior of the blood pressure was less constant and predictable than the behavior of the cisternal pressure. However, as a rule, the initial rise of cisternal pressure was accompanied by a fall in blood pressure. In instances in which the initial blood pressure was low, there was a tendency for this initial fall in blood pressure to be converted into a slight elevation. With the onset of the large permanent elevation of cisternal pressure there was occasionally a simultaneous progressive fall in the blood pressure but as a rule the fall of the blood pressure definitely followed the elevation of cisternal pressure as indicated in the graph. However, it was noted in some experiments that a reversal of the behavior of the blood pressure occurred when the level of the cisternal pressure approached 40 centimeters of water. Under these conditions the continued rise in the cisternal pressure was usually accompanied by a rise in the mean blood pressure. Further studies are needed to clarify these apparently anomalous relationships which seem to depend principally upon the relative levels of cisternal and blood pressures.

Data concerning the rise and fall of venous pressures in relation to cisternal and aortic blood pressures were too scanty to justify critical comment.

Ophthalmoscopic studies. There were 15 experiments in which adequate comparisons could be made between fundoscopic observations and cisternal as well as intra-aortic pressures.

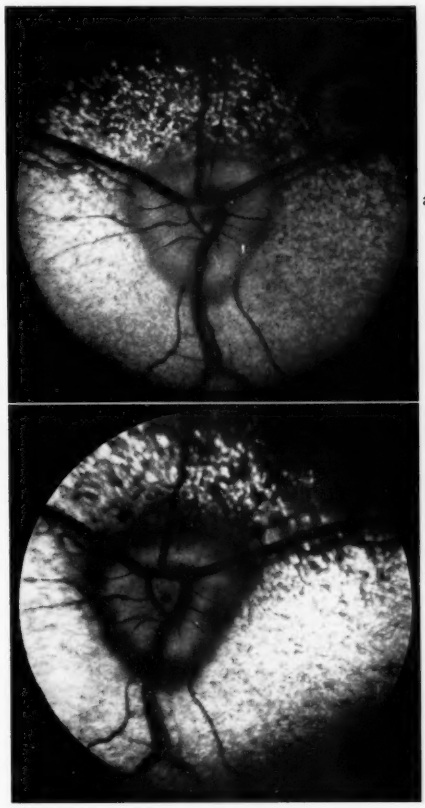


Fig. 1. a, The optic disc of a dog prior to the onset of papilledema. b, The same optic disc after the development of 3 diopters of papilledema. Note the increased prominence of retinal veins, the increased angulation of veins as they traverse the elevated margin of the disc, and the change in the contour and appearance of the margin of the disc.

Elevation of the optic discs from 1 to 6 diopters was observed in 10 experiments (Fig. 1). The average time interval between the initiation of the cerebral lesion by application of liquid nitrogen and the first signs of "choking" varied from 19 to 30 minutes with an average of about 25 minutes. This time interval was a little longer than that associated with the first evidence of the delayed persistent elevation of cisternal pressure and the results, thus far, indicate that the cisternal

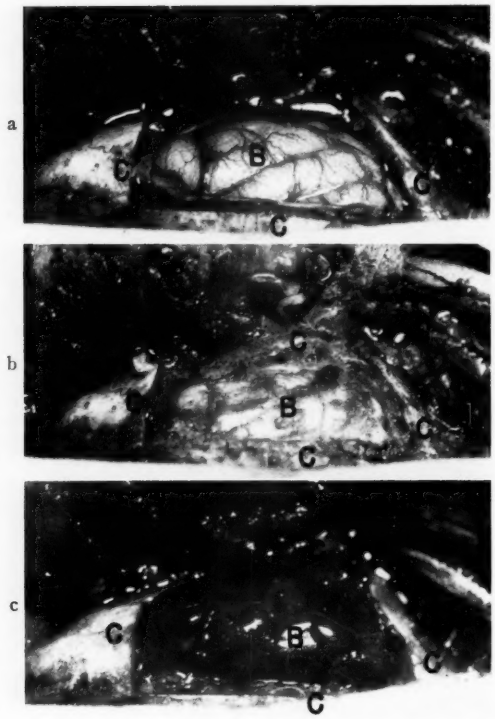


Fig. 2. a, The appearance of the normal parietal cerebral cortex as viewed directly after removal of a skull flap and before institution of the freezing procedure. *B* indicates the middle of the exposed cerebral cortex and *C* indicates the margins of the calvarium around the craniotomy wound. The skull flap was replaced and the customary freezing procedure was used. The skull flap was again removed. b, The frozen cerebral cortex exposed upon removal of the flap. The cortex was pale and stony hard. The contracted vessels contained stationary solid columns of blood. The frozen cerebral cortex illustrated in Figure 4 gradually thawed. c, As thawing proceeded, the congested edematous hemorrhagic cerebral cortex herniated through the surgical defect in the skull.

pressure usually rose more than 20 centimeters of water before measurable papilledema developed. As yet, however, there has been no consistent correlation between the magnitude of the diopterage of papilledema and the magnitude of elevation of the cisternal pressure above 20 centimeters of water. It was unlikely that the variable position of the lesions in the cerebral hemispheres were of importance in this regard, because the unilaterality of lesions led to no difference in the magnitude of papilledema in the two eyes. "Choked disc," when present, was always equal in each eye.

Four of the 15 animals had an unmeasurable disc elevation but by using parallax with the binocular ophthalmoscope an unmistakable impression of papilledema with moderate tortuosity and dilatation of veins was obtained. These 4 animals had gross evidence of mild subarachnoid hemorrhage. This degree of hemorrhage may have restricted the development of papilledema in agreement with observations by Griffith, Jeffers, and Fry. On the other hand, in 3 of the animals the cisternal pressure did not rise more than 16 centimeters of water. The fourth animal, which had a greater elevation of cisternal pressure, was studied before methods for protection of the cornea had been perfected and consequently the observations were uncertain.

One of the 15 animals had no increase in cisternal pressure and no papilledema.

Considerable variation in intra-aortic blood pressure occurred in this series of animals. Initial pressures varied within wide limits and the blood pressure under the different experimental conditions fluctuated a great deal during and after the development of papilledema. No consistent correlations between the blood pressure above shock levels and the magnitude of papilledema were noted. However, increases in blood pressure induced artificially were often accompanied by a proportionate increase in the diameter of retinal vessels.

Data concerning the relations between the level of the venous pressure and the development of papilledema were insufficient to justify comments at this time.

Several special observations were of interest to us. First, it was demonstrated that an artificially induced increase or decrease in cisternal pressure was usually accompanied by a corresponding change in disc elevation or caliber of vessels. Second, peripapillary edema was noted in association with great disc elevation and, at times, was accompanied by an apparent peripheral expansion of the disc. Third, during the development of papilledema a to-and-fro movement of red blood cells and occasionally a temporary reversal of flow of

the blood were observed in the large veins of the disc. These vessels frequently blanched with each inspiration. Finally, in every dying animal the large disc vessels were the first to blanch out, followed shortly by segmentation of blood columns in the more peripheral vessels. With the blanching of disc vessels, just before death, a definite flattening of the nerve head of previously "choked discs" occurred. Death was accompanied by a discward flow of blood, both in the arteries and veins. This continued for several minutes after cessation of recorded arterial pulsations.

Gross pathologic studies. Orientation experiments were done to permit direct visual observation of the sequence of changes in the cerebral cortex during freezing and thawing. In doing this a parietal skull flap was turned back and then replaced (Fig. 2). The tip of the freezing instrument was placed against the external surface of the flap and the usual freezing procedure was carried out. The skull flap was then removed and the brain immediately beneath it was noted to be pale and stony hard with blood apparently motionless and frozen in the pial vessels (Fig. 2). The exposed cerebral cortex began to soften in about 10 minutes. The blood vessels dilated and blood began to ooze into the perivascular tissues. Gradually, the entire cortex changed in color from pale gray to pink to deep purple. This congestion and perivascular hemorrhage was accompanied by edema and increased friability of tissue so that the swollen damaged brain herniated through the surgical defect in the skull (Fig. 2). About 20 to 25 minutes passed before the sequence of changes was completed. Figure 3 indicates the appearance of the lesion after removal of the brain from the skull.

Under the customary experimental conditions, the skull was intact. The lesions which developed were similar to the final lesion described in the preceding paragraph (Figs. 4, 5, and 6). They appeared as sharply circumscribed soft areas in the cerebral cortex. They varied in color from grayish-red to dark purplish-red. Pial vessels within the area occupied by the lesion were dilated. Extravasation of blood into the perivascular arachnoidal tissue was always present within the boundaries of the lesion but significant oozing of blood into the subarachnoid space beyond the margin of the lesion seldom occurred.

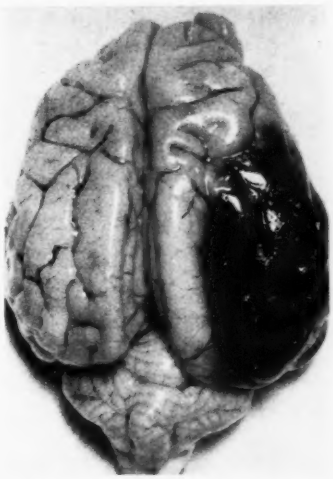


Fig. 3. After thawing of the cerebral cortex shown in Figure 2 was completed, the animal was sacrificed and the brain removed. This photograph shows the external appearance of the lesion. This is to be compared with the acute closed cerebral lesions illustrated in Figures 4, 5, and 6. Presumably, the sequences in the development of lesions produced without turning back a skull flap were essentially the same as those shown in Figures 2 and 3.

Coronal sections through the lesions disclosed variable depths of involvement of the gray and white matter (Fig. 7). In general the involved tissues were congested, hemorrhagic, edematous, soft, and friable. The lines of demarcation between normal and damaged tissue were very sharply defined. These lines of demarcation indicated in most instances that the lesions were in the shape of a truncated cone or a hemispherical segment with the maximum diameter at the surface of the brain and minimum diameter at the point of deepest penetration (Fig. 7). The superficial lesions principally involved the gray matter. This involvement was not strictly linear but seemed to affect the gray matter between the sulci more than the white matter at a corresponding depth (Fig. 7). This appearance was due either to the greater vascularity and sensitivity of cortical structure or to a greater resistance and lesser vascularity of the structure of the subcortical white matter. Most

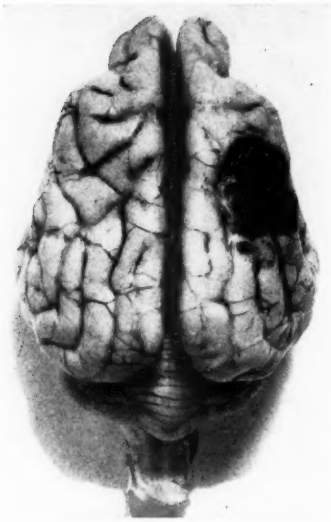


Fig. 4.

Fig. 5.

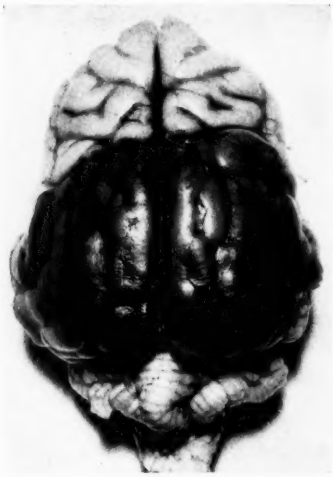


Fig. 6.

Fig. 4. A small acute parietal lesion produced by freezing the brain through the intact calvarium. Note the discoloration due to cortical congestion and hemorrhage. Despite the conspicuous perivascular hemorrhage, the margins of the lesion were sharp and there was, as usual, no significant escape of blood into the general subarachnoid space. A cross-section of this lesion is shown in Figure 7.

Fig. 5. Three acute cerebral lesions produced in succession, varying only the time of contact between the cold isopentane and the skull. Lesions similar to the left parieto-occipital lesion were usually produced in 2 to 3 minutes. Lesions similar to the left frontoparietal lesion were usually produced in 3 to 5 minutes. Lesions, similar to the right frontoparieto-occipital lesion were usually produced in about 10 minutes and represent about the maximum size of lesions when the circular contact area of the cold isopentane with the calvarium was 10 millimeters in diameter. The volumes of cerebral damage in the 3 lesions were as follows: 0.1, 8.3, and 17.5 per cent of the volume of the whole brain.

Fig. 6. The maximum degree of reproducibility of successive lesions produced by freezing the 2 cerebral hemispheres through the intact calvarium. These bilateral parieto-occipital lesions had almost identical surface areas (10.4 and 9.9 sq. cm.), depths (10 and 11 mm.), volumes, and anatomic locations. The character and magnitude of cerebral damage, as judged grossly and microscopically, were essentially the same. The total volume of cerebral damage was 23.5 per cent of the volume of the whole brain.

lesions extended through the gray matter and for a depth of several millimeters into the white matter (Fig. 7). Occasionally, the wall of the lateral ventricle was involved with consequent intraventricular hemorrhage.

Lesions of different sizes were produced at will (Figs. 4, 5, and 6). Some were quite small and discrete (Fig. 4), others were large and involved almost the entire cerebral hemisphere (Fig. 5). Occasionally, bilateral lesions of large dimensions were made (Fig. 6). In each instance they were sharply circumscribed.

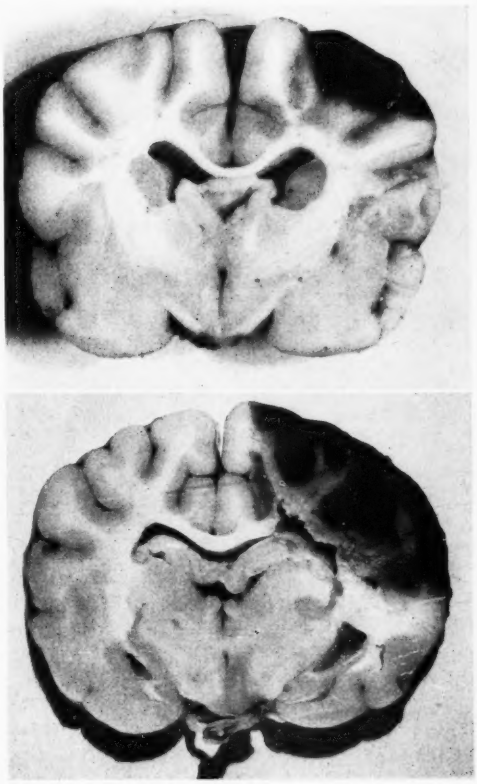
Microscopic pathologic studies. After fixation of the brain in formalin, coronal sections, 5 millimeters in thickness, were made. Representative blocks of tissue were taken from the lesions produced by freezing. Ordinarily, these blocks included the leptomeninges, cerebral cortical gray matter, subcortical white

matter, and the zone of transition between normal and abnormal tissue at the margins of lesions. After customary technical preparation, celloidin or paraffin sections stained with hematoxylin and eosin became available for study. In special instances, stains for the demonstration of myelin sheaths and axis cylinders were made.

Inasmuch as all experiments of this report were only a few minutes to a few hours in duration, the principal microscopic findings were referable to the acute degenerative changes produced by freezing and the early effects secondary to these changes.

When the animal was sacrificed shortly after the cerebral lesion had thawed, the general architecture of the brain showed only minor changes (Fig. 8). These consisted of shrinkage of nerve cells in the cerebral cortex and agglutination thrombi composed of clumps of erythrocytes or leucocytes in the capillaries and small blood vessels in the cerebrum and leptomeninges.

When the animal was sacrificed several hours after the cerebral lesion had thawed, the histologic changes varied in accordance with the magnitude of the lesion and the lapse of time after thawing (Fig. 9). In general there was a progressive cytolysis of cortical nerve cells so that within a few hours, nothing more than indistinct remnants of cell bodies and their processes could be distinguished. The glial cells, fibrocytes, and endothelial cells were more resistant and many seemed to remain structurally unimpaired but there is a question as to whether they retained full viability. Also, there was a progressive vasodilatation which did not affect all vascular arborizations equally. In connection with the variable vasodilatation there was a variable amount of occlusion of small vascular channels with agglutinated masses of erythrocytes or leucocytes. Thrombi of the latter principal composition were often conspicuous. As a rule, these signs of vascular involvement were accompanied by perivascular hemorrhage. This bleeding was increasingly pronounced distally along the course of larger vessels and in relationship to the capillary plexuses, especially in the gray matter (Fig. 9). In addition to frank hemor-



a, above
b, below

Fig. 7. a, Coronal section of the brain illustrated in Figure 4. This was a small surface parietal lesion and the depth of penetration was correspondingly small. Note the sharp margins between damaged and normal brain. Also, the general shape of cross-sections of all lesions is illustrated. The curvatures of the surface areas as well as the margins of the lesions in depth led to an appreciable error in the calculation of the volumes of cerebral damage. However, about the same degree of error was inherent in all calculations and, therefore, was neglected for present purposes. The volume of cerebral damage in this instance was 1.5 per cent of the whole brain. b, Coronal section of a brain in which a large unilateral lesion was produced by freezing through the intact skull. This lesion extended to the wall of the lateral ventricle. In such instances, intraventricular hemorrhage was occasionally demonstrated. Note the characteristic tendency for congestion and hemorrhage to be excessive in the cortical gray matter. Changes in the white matter, however, were always found at similar levels and depths. The resemblance between lesions of this type and those produced by a high order of dynamical trauma was very great. The volume of cerebral damage in this instance was 9.1 per cent of the volume of the whole brain.

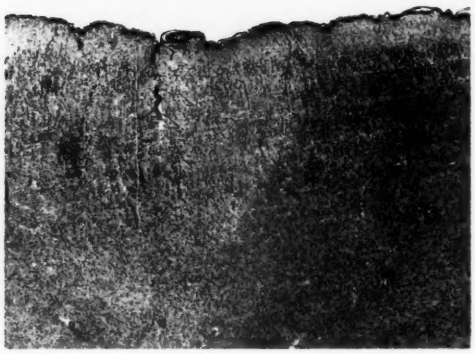


Fig. 8. This is a low power photomicrograph of the margin of an early acute lesion in the cerebral cortex. This animal died 2 hours after the lesion produced by freezing had thawed. The light colored area in the left half of the photograph was occupied by the lesion. The highly cellular structure of normal cortical gray matter occupied the right half of the photomicrograph. Note the sharp line of demarcation between damaged and normal cortical tissue. Some nerve cells in the area of damage have disappeared by lysis. All remaining nerve cells were shrunken and distorted. Capillaries were dilated and there were tiny perivascular hemorrhages.

Fig. 9. A medium power photomicrograph of a lesion in the cerebral cortex, 6 hours older than that shown in Figure 8. The vessels of the pia mater and one large vessel in the cortex contained agglutination thrombi composed mostly of leucocytes and fibrin. The pallor and separation of structure in the periphery of the cortex was attributable to edema. The deeper circumscribed pale areas were sites of vasodilatation, edema, and perivascular hemorrhage. Distorted remnants of nerve cells remained throughout the cortical field. Several hours beyond the duration of this lesion passed before the final stages of cellular degeneration and early stages of repair became apparent.

rhage there was extravasation of serum free from cellular elements and irregular separation of structures indicative of interstitial edema. These latter effects were more easily recognized in the white matter (Fig. 10). In older lesions, extravascular leucocytic migration of a diffuse cortical distribution was apparent but total breakdown of tissue structure with the expected local massive leucocytic infiltration had not yet occurred.

Volume per cent of cerebral damage. The measurement of the volume of the brain was fairly accurate. The volumes varied from 53.5 to 119.0 cubic centimeters. The measurement of the volume of the lesions was less accurate and at best was only a first approximation. Sources of error in exact measurement were usually attributable to simplified calculation which did not take into account the variable curvatures of the surface and intracerebral part of each lesion (Figs. 4 and 7). The variable contour of convolutions and sulci as well as the variable degrees of congestion, hemorrhage, and edema introduced other sources of error (Fig. 7). It is hoped that better measurements can be obtained in the future by the use of more quantitative methods involving the determination of the amount of excess water and blood in the hemisphere containing the lesion. Some such evaluation of the space-occupying or expanding characteristics of each lesion would seem to be required. Despite the sources of error the volumes of cerebral damage, which varied from 0.1 to 34.0 per cent of the whole brain, were fairly closely correlated with the elevation of cisternal pressure. The relation was fairly linear when lesions were small but when lesions were large the correlation was less exact. Final correlations will require more data.

DISCUSSION

In any large group of patients with head injuries there are seldom any 2 patients with identical lesions. The variables of concussion, cranial fracture, intracranial hemorrhage, cerebral contusion, cerebral edema, intracranial pressure, circulatory competence, and extracranial lesions introduce great difficulty

in the interpretation of the pathogenesis of clinical manifestations. The effectiveness of one or another form of treatment is equally difficult to evaluate and it must be admitted that the treatment is, for the most part, empirical.

It seems clear that a scientific basis for treatment should be established. In order to do this, each important variable contributing to the symptomatology of patients with head injuries should be evaluated separately. A step in this direction has been taken in the present experiments. Discrete localized lesions in the cerebrum of dogs were produced by freezing the brain without interrupting the continuity of the calvarium or introducing concussional and other traumatic variables incidental to mechanical trauma. By use of standardized methods the breadth, depth, and location of the lesions were well controlled. Lesions were qualitatively and quantitatively reproducible in the same animal or successive animals. The principal changes within the lesions were attributable to vascular damage although acute degeneration of other cerebral structures within the zone of injury occurred. Congestion, edema, perivascular hemorrhage, and necrosis of tissue were conspicuous so that the gross appearance of the lesions was similar to that commonly encountered as a result of cerebral contusion, arterial thrombosis, extensive venous thrombosis, or intracerebral hemorrhage. Bleeding beyond the boundaries of the lesions was ordinarily insignificant or inapparent.

The lesions which were produced provided, therefore, a relatively simple approximation to those occurring in the brain as the result of trauma or certain nontraumatic disorders. They were so sharply defined that quantitative measurements could be made and the volume per cent of cerebral injury calculated with considerable accuracy. Furthermore, it was possible to undertake measurements in the dog which had been difficult or impossible in our previous experience with rabbits. Continuous electronic recording of the cisternal pressure and intra-aortic blood pressure with manometric recording of inferior vena caval blood pressure was done. Fundoscopic observations were made.

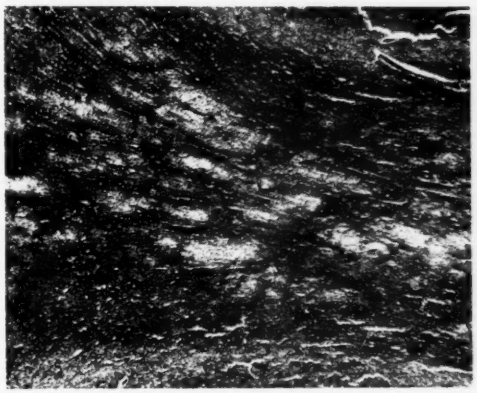


Fig. 10. This medium power photomicrograph of the subcortical white matter shows multiple pale areas. These indicate zones where edema and extravasation of serum have produced a separation of the axones and supporting structures of the fiber tracts. Hemorrhage was usually less conspicuous in the white matter than in the gray matter while edema was more easily recognized in the white matter. Edema of lesser degree than that illustrated was very difficult to distinguish, microscopically.

We do not believe that the experiments thus far justify final conclusions concerning the exact relations among these several quantitative measurements. Suffice it to say that the behavior of the system under investigation, analyzed by the methods described, should provide a reproducible experimental situation for reliable evaluation of the influence of one or another form of treatment of a localized acute expanding intracerebral lesion characterized by congestion, hemorrhage, edema, and necrosis.

SUMMARY AND CONCLUSIONS

1. A method was developed for freezing the brain of the dog by application of an instrument containing isopentane cooled by liquid nitrogen to the external surfaces of the intact calvarium.

2. By use of a standard area of contact between the cold isopentane and the calvarium and by increasing the duration of contact from 2 to 10 minutes increasingly large volumes of brain were frozen.

3. During freezing of the brain there was a slight transient rise in the cisternal pressure accompanied by a temporary slight fall in intra-aortic blood pressure.

4. After disengaging the instrument containing cold isopentane and liquid nitrogen from the skull, the volume of frozen brain began to thaw. As thawing proceeded over a period of several minutes progressive vasodilatation, perivascular hemorrhage, softening, and edema developed in the previously frozen volume of brain. Each volume of injury was sharply circumscribed and similar in character wherever located in the convexity of the frontal, parietal, or occipital lobes of one or both cerebral hemispheres.

5. The development of congestion, hemorrhage, and edema was accompanied by an elevation of cisternal pressure to an average maximum value of 50 centimeters of water in experiments with lesions of moderate dimensions. This maximum value was reached within 30 to 60 minutes after production of the lesion and persisted or slightly decreased over a period of several hours.

6. The mean intra-aortic blood pressure usually fell as the cisternal pressure increased to moderate levels but as the cisternal pressure approached 40 centimeters of water the mean intra-aortic blood pressure usually began to rise.

7. Continuous fundoscopic observations disclosed the progressive sequences in the development of papilledema as thawing of the frozen brain occurred. Disc elevations, always equal in both eyes, varied from less than 1 to as much as 6 diopters. Measurable papilledema did not develop when the cisternal pressure was less than 20 centimeters of water. Though papilledema developed consistently when cisternal pressures were at higher levels, the diopterage of disc elevation could not be correlated quantitatively with the increment of cisternal pressure.

8. These methods and observations provide a dependable quantitative basis for further study of the pathophysiology and rational treatment of acute closed cerebral injury.

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AN EXPERIMENTAL EVALUATION OF PULMONARY FUNCTION AND LUNG SUBSTANCE DISTAL TO TRANSECTION OR RESECTION OF TRACHEOBRONCHIAL SEGMENTS

LAWRENCE B. KIRILUK, M.D., WALTER A. RICKER, JR., M.D., and
K. ALVIN MERENDINO, M.D., F.A.C.S., Seattle, Washington

THE feasibility of tracheobronchial resections with reconstruction has been established experimentally and clinically. Such procedures are designed to preserve normal lung tissue distally. The fact that such operative procedures can be done is of little import unless it can be demonstrated that the distal lung is healthy and is capable of performing its normal respiratory function.

Although some gross and microscopic studies have been reported, functional evaluation and a correlation of function with gross and microscopic changes have not been done. This study was undertaken in an attempt to evaluate the gross pathologic, histologic, and functional changes following the surgical reconstruction of the tracheobronchial tree.

MATERIALS AND METHODS

The animals studied are the same as those reported in previous publications (1, 2). Studies were made in order to evaluate the functional and pathologic status of lung distal to the site of transection or resection of the trachea or bronchus. The following studies were done: (1) spirometry—differential, total, electrophrenic respiration; (2) other physiologic tests—contralateral pulmonary artery ligation, contralateral pneumonectomy; (3) gross examination of specimens; (4) microscopic studies.

The changes in pulmonary function distal to the site of transection or resection of the trachea or bronchus was investigated by total and differential spirometry. Adult mongrel dogs were anesthetized with 30 milligrams of nembutal per pound of body weight. The animals then were placed in a supine position and spirometry was done, an endotracheal tube of various sized Zavod catheters being used. The Zavod catheters were modified by cutting off the distal portion just beyond the balloon. The shortened tip facilitated the placement of the catheter within the left main stem bronchus and resulted in a free exchange of oxygen. A double spirometer filled with oxygen was used. The animals were allowed to breathe for at least 5 minutes prior to recording for purposes of stabilization. A 4 minute record (Fig. 1a and b) then was obtained. The minute volume (M.V.) and minute oxygen consumption (M.O.C.) either total or differential were computed. The respiratory efficiency (R.E.) was calculated from the formula:

$$\text{R.E.} = \frac{\text{c.c. of oxygen uptake per minute (M.O.C.)}}{\text{c.c. of respired air per minute (M.V.)}} \times 100.$$

All volumes were corrected to standard temperatures and pressures. The respiratory efficiency was calculated for each dog as a whole and not per kilogram of body weight since all of the animals in each group were studied preoperatively and postoperatively. There was no great variation in the body weights of the animals during the entire study.

Function studies. Respiration efficiency was calculated for a series of 32 normal animals, 20 animals subjected to electrophrenic respiration, and in 36 animals subjected to bronchial transection, bronchial resection, tracheobronchial resection, pulmonary artery

From the Department of Surgery, University of Washington School of Medicine, Seattle, Washington.

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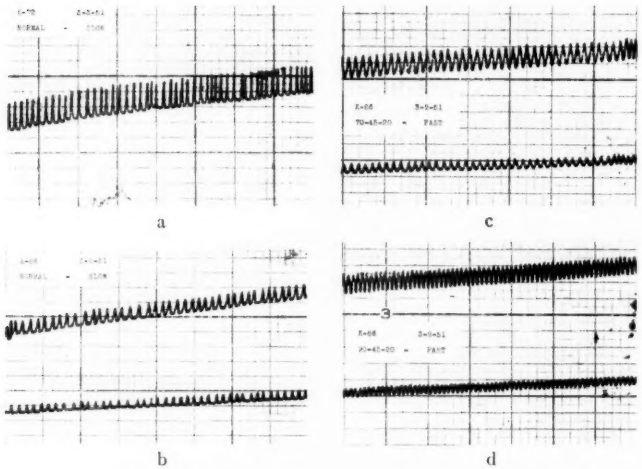

Fig. 1. a, Spirometric tracings in a normal dog via endotracheal tube. Each small square horizontally represents 6 seconds and vertically represents a 50 cubic centimeter volume. b, Tracings of differential spirometry with a Zavod catheter in a normal animal. The right lung respiration is represented by the upper tracing and the left lung by the lower tracing. c, Electrophrenic stimulation: differential spirometry when the right phrenic nerve is stimulated. The stimulator is set at rate 70, distribution 45, and depth 20. Horizontally, each small square represents 3 seconds. d, As in c, except that the stimulator is set at 90, 45, and 20, respectively.

ligation, pneumonectomy, or combinations of these procedures.

Spirometry in conjunction with electrophrenic respiration represents an attempt to evaluate the function of a lung subjected to increased stress. An electrophrenic stimulator was used. Cutaneous stimulation of the right phrenic nerve only was done. An attempt was made to control the rate and depth of respirations (Fig. 1c and d).

Respiratory function of lung distal to the resection of a stem bronchus was tested also by ligating the contralateral pulmonary artery in 10 animals, or by doing a contralateral pneumonectomy in 20 animals.

Gross tissue studies. A gross examination was made of 135 lung specimens. Observations were made of the appearance, texture, and contour of each specimen. Direct comparisons were made of the lungs operated upon and those not operated upon. These specimens were obtained from animals subjected to bronchial transection or resection with or without contralateral pulmonary artery ligation, bronchial transplantation, bronchial autografting, carinal resection, resection of the carina combined with pneumonectomy or tracheal resection. The lung specimens were obtained postoperatively at periods varying from several hours to 666 days.

Microscopic. Forty-five lung specimens were studied microscopically. Sections were taken of representative "normal appearing" lungs and in all cases in which abnormalities were suspected. The specimens were obtained postoperatively at periods varying from several hours to 519 days.

RESULTS

Spirometry. The results of spirometry are summarized in Table I. Total respiration with an endotracheal tube was studied in 18 dogs and differential spirometry by means of a Zavod catheter was done in 17 animals. Both total and differential spirometry was done in the same animal in certain instances. The minute volume during differential spirometry was slightly more than the minute volume observed when an endotracheal tube

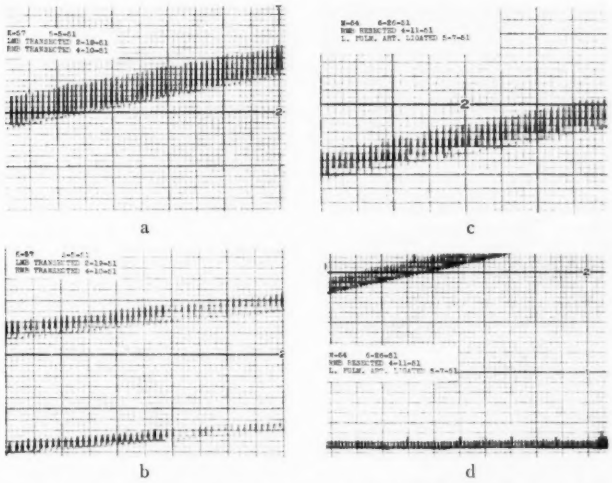

Fig. 2. a, Endotracheal spirometry in an animal subjected to bilateral stem bronchus transection with direct anastomosis. Horizontally, each square represents 6 seconds, and vertically each small square represents 50 cubic centimeters of respired volume. b, Differential spirometry in the same animal. c, Endotracheal spirometry in an animal with the right stem bronchus resected and directly anastomosed, and the left pulmonary artery ligated. d, Differential spirometry in the same animal as in c. There is no oxygen consumption by the left lung.

as used. The minute volume of the right ng was greater than that of the left lung. he relationship of the respired air by endo- racheal tube to that respired by the Zavod atheter, when right and left lungs were meas- red separately, remained essentially the me throughout the entire experiment. Any otable change in these values would be sig- ificant. In the normal animal, the average spiratory efficiency as obtained by endo- racheal tube was 4.8. When the Zavod atheter was used, the average respiratory efficiency was 5.8 for the right lung and 4.4 or the left lung.

Of 20 animals studied in conjunction with electrophrenic stimulation, 7 were endotra- cheal and 13 differential recordings. At- tempts were made to determine the func- tional response of the lungs by subjecting the animals to abnormal stress by increasing the rate of stimulation. When the endotracheal tube was used with the rate of the stimulator set at 70, the respiratory rate was approxi- mately double that of normal, and the re- spired volume was increased by approxi- mately 50 per cent. The minute oxygen con- sumption (M.O.C.) was decreased and the respiratory efficiency was reduced to 1.7, ap- proximately one-third of normal. When the rate was set at 90 the respiratory rate was increased to approximately 4 times that of normal, and the respired volume was more than doubled; but the respiratory efficiency was decreased to 1.3, approximately one- fourth that of normal. During differential spirometry the same relationship existed but to a lesser degree. In comparing the effects of an increased respiratory rate effected by electrophrenic stimulation with normal breath- ing in the same animal, electrophrenic stimu- lation consistently resulted in an increased minute volume, reduced minute oxygen con- sumption which resulted in a decreased res- piratory efficiency. In the experiments with the electrophrenic stimulator, only the right phrenic was stimulated. An interesting ob- servation was made; viz., that in spite of a disproportionate increase in minute volume of the right lung when compared to the left; the oxygen uptake of the right lung was less

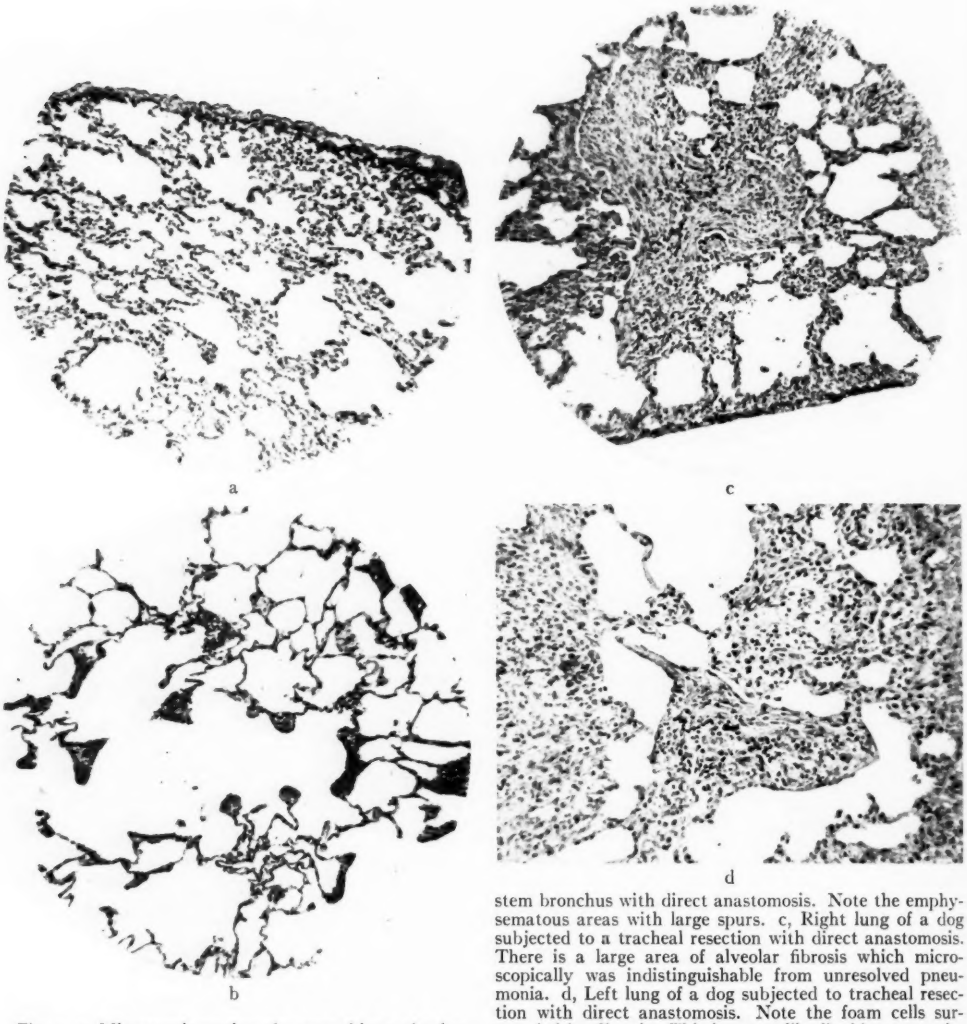

Fig. 3. a, Microscopic section of a normal lung of a dog. b, Right lung of a dog subjected to resection of the right stem bronchus with direct anastomosis. Note the emphysematous areas with large spurs. c, Right lung of a dog subjected to a tracheal resection with direct anastomosis. There is a large area of alveolar fibrosis which microscopically was indistinguishable from unresolved pneumonia. d, Left lung of a dog subjected to tracheal resection with direct anastomosis. Note the foam cells surrounded by fibrosis. This is not unlike lipoid pneumonia. Magnifications: a, b, c, ×42.5. d, ×100.

than that of the left. This will be alluded to later.

Spirometry, both total and differential, was done on animals previously subjected to bronchial transection or resection. These studies revealed no consistent significant change in respiratory efficiency when preoperative and postoperative, or right to left lung records were studied and compared (Fig. 2a and b). Following the resection of the carina or the carina and the left lung, the minute volume, minute oxygen consumption, the respiratory efficiency remained approximately the same. There was no tendency toward oxygen uptake by the left lung in those animals in which the left pulmonary artery was ligated and in which the right stem bronchus had been previously resected (Fig.

TABLE I.—SPIROMETRIC STUDIES IN NORMAL DOGS, DOGS SUBJECTED TO ELECTROPHRENIC RESPIRATION, AND DOGS SUBJECTED TO VARIOUS SURGICAL PROCEDURES OF THE TRACHEOBRONCHIAL TREE

Procedures		No. of cases	Average wt. kgm.	M.V.			M.O.C.			R.E.		
				Tracheal	Rt. lung	Lt. lung	Tracheal	Rt. lung	Lt. lung	Tracheal	Rt. lung	Lt. lung
Normal		32	15.0	1698 (18)*	1142 (17)	591	76.6	66.4	25.9	4.8	5.8	4.4
Electrophrenic respiration in normal dogs	70	20	13.1	2579 (7)	1975 (13)	957	41.0	50.0	29.3	1.7	2.6	3.4
	90	20	13.1	3430 (7)	2114 (13)	962	40.1	43.9	26.2	1.33	2.1	3.1
Transection and reconstruction of both stem bronchi	Preop.	2	16.8		960	603		51.9	43.1		5.4	6.6
	Postop.	2 (4)	15.3	1392	1094	576	79.0	56.5	23.0	5.7	5.0	4.1
Resection and reconstruction of stem bronchi (4 lt.; 10 rt.)	Preop.	14	15.7	1916	1121	565	91.8	67.9	21.0	4.2	6.5	4.2
	Postop.	14 (17)	15.5	1463	1186	556	88.4	51.0	25.0	6.3	5.8	5.0
Resection of carina and/or one lung with reconstruction	Preop.	5	9.6	1178			49.0			4.7		
	Postop.	5 (8)	9.5	1233			54.0			4.4		
Left pneumonectomy with previous resection and reconstruction of rt. stem bronchus	Preop.	7	14.6		1003	550		52.9	18.2		6.0	3.9
	Postop.	7 (8)	13.5	1214			68.0			5.6		
Left pulmonary artery ligation with previous resection and reconstruction of rt. stem bronchus	Preop.	8	15.3	2612	1173	576	60.7	60.9	19.9	4.5	5.8	3.8
	Postop.	8 (9)	15.3	1465	1085	510	67.6	71.3	0.0	5.5	6.3	0.0

*The number in parentheses indicates the number of recordings.

2c and d). The animals subjected to a resection of the right stem bronchus and later to a contralateral pneumonectomy showed no significant change in respiratory efficiency.

Other physiologic tests of function. Contralateral pulmonary artery ligation was done in 10 animals which had previously undergone bronchial transection or resection. No adverse effect was noted on the health or activity of the animals following recovery from anesthesia. One animal died and the autopsy revealed a hemorrhagic infarction of the entire left lung. This was attributed to pulmonary artery ligation. Contralateral pneumonectomy was performed in 20 animals which had previously undergone bronchial transection or resection. Eleven left pneumonectomies were performed with no mortality. Seven of these had previous isolated pulmonary artery ligations. Nine right pneumonectomies were done with 5 deaths. Four deaths were due to pneumonias; 3 of these animals succumbed on the day of surgery or shortly thereafter. The other animal was sacrificed 6 weeks postoperatively because of severe pneumonia. The fifth death occurred 5 days postoperatively. No cause of death could be established. The remainder of the animals did exceptionally well until the study was terminated.

Gross studies. Of 135 gross lung specimens studied, 101 animals had normal appearing lungs grossly. Twenty-six revealed some degree of pneumonitis, this included: 6 dogs dying of distemper; 7 dogs subjected to bronchial autografting, all of which were failures and all exhibited pneumonia; 1 dog died with an infarct of the left lung following ligation of the left pulmonary artery. Five dogs had gross emphysema and 3 showed some degree of atelectasis. With the exception of the dogs developing distemper and those subjected to autografting, pneumonia was most frequent in the cases of resection where the anastomotic line was under tension and gradual separation of the suture line occurred. Granulation tissue was invariably present and infection frequent. Atelectasis and emphysema were noted grossly in several cases in which stenosis had occurred at the site of anastomosis.

Microscopic studies. Forty-five lung specimens were studied microscopically and all of the gross pathologic diagnoses were confirmed. A wide range of pathologic changes was noted in addition to the obvious changes. The

microscopy can be presented only in general terms, since many cases exhibited various types and degrees of pathology within the same lung. Emphysema in varying degrees and stages was the most frequent unsuspected condition. It is unfortunate that routine sections were not taken in every case, since approximately one-third of the grossly normal lungs studied microscopically revealed some evidence of emphysematous change. The changes varied from an occasional dilated alveolus with small spurs to diffusely dilated alveoli and numerous large spurs (Fig. 3b). The occurrence of alveolar and interstitial fibrosis was frequent and in most cases unsuspected. Usually the fibrous tissue was minimal and patchy, but instances were noted in which large areas of lung tissue were involved much in the manner of unresolved pneumonia (Fig. 3c). The fibrotic process in some cases was associated with a mild chronic interstitial inflammatory reaction.

Sections of lungs taken from the side not operated upon revealed the same emphysematous and fibrotic changes as were seen in the lung distal to the site of surgical intervention. In general, if the cases which exhibited gross pathologic changes were excluded, the lungs operated upon and those not operated upon were indistinguishable microscopically.

In 2 cases the alveolar walls showed patchy, prominent thickenings and accumulations of macrophages filled with vacuoles as seen in lipid pneumonia (Fig. 3b). No explanation for this is proposed. Cases in which stenosis or stricture of the bronchial lumen occurred revealed atelectasis, varying degrees of pneumonitis, and mucous plugs within the bronchial tree distal to the obstructive mechanism. Inflammatory processes within the tissue studied varied from a mild chronic pneumonitis to an acute pneumonia of the consolidating type.

DISCUSSION

Of necessity, spirometric studies in the dog are somewhat crude. The animal must be anesthetized. This alone is a respiratory depressant. No attempt was made to place the animals under basal conditions. It was believed that comparisons of respiratory efficiency could be made, approximately under the same conditions.

Spirometry in conjunction with electrophrenic stimulation of the right phrenic nerve was done only in normal animals. Upon initiation of this program it was believed that by controlling the rate of respiration, some of the inconsistencies observed in the anesthetized dogs would be obviated and thereby be of aid in the evaluation of respiratory function. However, by the utilization of the cutaneous stimulator on the right phrenic nerve alone, neither the depth nor the phase interval could be consistently controlled. In addition, the contralateral lung (left) did not respond proportionately to stimulation as did the lung (right) on which the phrenic nerve was stimulated.

By increasing the rate of respiration with electrophrenic stimulation of the phrenic nerve, the respiratory efficiency was severely decreased. When the endotracheal tube was used the minute volume was increased, the oxygen consumption decreased, and respiratory efficiency reduced. Under similar circumstances when differential spirometry was performed, the minute volume was increased bilaterally, however the increase of the right lung was disproportional to the left. This suggests that the contralateral spread of the stimulatory response does not appear to be sufficient to produce an identical respiratory effort bilaterally. However, in spite of the increased minute volume, the oxygen consumption of the right lung decreased while the oxygen consumption of the left increased. While both right and left lungs individually revealed a reduced respiratory efficiency. The reduction in efficiency of the left lung was relatively less than the right and was due not to a reduced oxygen consumption, which was actually increased, but to a greater relative increase in minute volume.

A possible explanation for this phenomenon may be related to the inadvertent overflow stimulation of the right vagus nerve which lies adjacent to the phrenic. There is physiologic evidence that the vagus nerve may exert a constrictor effect on coronary vessels. It is conceived that a similar arrangement may be

present with regard to the pulmonary vasculature. In the presence of vasospasm in the capillary areas the resultant effect would be the deviation of pulmonary flow away from the capillary bed where gaseous exchange takes place; thereby shunting unoxygenated blood from the right heart through small collaterals directly into the vessels on the left side of the circulation.

In the study of this problem by spirometry some variations occurred from animal to animal and in the same animal from day to day. A standardized dosage of anesthetic agent based upon kilogram of body weight may produce relatively wide ranges of response depending upon the animal's state of hydration and feeding on any particular day. However, in many cases a comparison of the respiratory efficiency of the right to left lung could be made before and after surgical procedures with the side not operated upon serving as a control. Consequently, a base line was obtained for the interpretation of the variations. It can be stated that the spirometric studies revealed that the lung distal to a transection or a resection retained a respiratory efficiency approximately equal to that prior to surgery.

Other gross methods of establishing the respiratory adequacy of pulmonary tissue distal to tracheobronchial reconstructive procedures included contralateral pulmonary artery ligation and contralateral pneumonectomy.

Following the ligation of the contralateral pulmonary artery to an apparently normal lung, spirometric studies showed no oxygen uptake, and an unchanged minute volume. Observation periods up to 45 minutes done at 1 and 2 month intervals revealed no perceptible oxygen uptake. This finding is consistent with the experience of others. It is apparent that the survival of the animal was entirely dependent upon the ability of the pulmonic tissue distal to the site of tracheobronchial reconstruction to respire in a relatively normal manner. The same is true for those animals subjected to contralateral pneumonectomy.

Contralateral pneumonectomy was performed in 20 animals, 15 survived. Four deaths were due to pneumonia during the same week. It is possible that unsuspected inflammatory areas within the lung may under the stress of multiple operative procedures result in a flare-up of the process with a lethal pneumonia.

Five animals undergoing a resection of the carina, or the resection of the carina and the left lung were studied to detect the possible effects of a decreased dead space on respiratory efficiency. No significant changes were noted. The respiratory efficiency of a lung in its normal position and occupying a normal space, determined by differential spirometry, was not grossly different from the respiratory efficiency of the same lung in a different position and occupying a larger space, as occurs following a contralateral pneumonectomy.

The presence of unsuspected interstitial and alveolar fibrosis and of ruptured alveolar walls with spur formations was of considerable interest. The fibrotic lesions were indicative of healing or healed reactions due to inflammation or trauma incident to surgery. A mechanical respirator without manometric control was used during surgery. Consequently, the actual pressures exerted on inflation of the lungs were unknown. By observation, no overdistention was thought to have occurred. However, it is apparent that overdistention of the alveoli did occur. The ruptured walls, the development of spurs, the presence of localized emphysema, and the initiation of fibrotic lesions clearly support this assumption. Furthermore, the bilaterality of the lesions in animals subjected to an operation and reconstruction on only one bronchus indicates that the lesions are unrelated to the operative procedure itself. These findings clearly indicate the necessity for using carefully regulated pressures in any procedure involving the artificial ventilation of pulmonary tissue.

A direct correlation of gross and microscopic studies to function studies cannot be made in this study. The majority of the animals recovered from surgery readily. They displayed no evidence of illness, gained weight, and engaged in normal activity. Spirometric studies revealed no significant changes in res-

piratory efficiency between the preoperative and the postoperative status of the lung. At postmortem, the majority of the lungs were considered to be within normal limits on gross examination. However, microscopy revealed the frequent occurrence of emphysema and fibrosis, both in varying degrees. Apparently the lungs have a large reserve capacity and, therefore, pathology, which is considered to be of moderate magnitude microscopically. Neither can be demonstrated by observation of the tissues grossly nor by spirometry under the conditions of this study.

SUMMARY AND CONCLUSIONS

Spirometric studies done in dogs reveal that the respiratory function of pulmonary tissue distal to bronchial transection and tracheobronchial resection with reconstruction is not grossly altered. Contralateral pulmonary artery ligation and contralateral pneumonectomy following resection and reconstruction procedures provided a severe test of function on the lung of the reconstructed side. The survival of these animals without apparent disability established without doubt the respiratory function of the distal lung. Spirometric studies of the lungs subjected to pulmonary artery ligation revealed no oxygen uptake up to 2 months postoperatively.

Microscopy, in addition to confirming the gross impressions at autopsy, revealed varying degrees of pathologic changes which were unsuspected. These changes consisted of small areas of fibrosis and inflammation. Evidence of emphysema on both the sides operated upon and those not operated upon was believed to be due to possible overdistention of the lung at the time of surgery.

In normal animals, subjected to electrophrenic stimulation (right phrenic) by increasing the respiratory rate 2 to 4 fold the minute volume was increased, the oxygen consumption decreased, and the respiratory efficiency was reduced. The reduction in oxygen consumption and respiratory efficiency was directly proportional to the increase in rate. The respiratory efficiency of the right lung was decreased to a greater extent than the left. A possible explanation involves the possibility of "overflow" stimulation of the right vagus nerve which may exert a constrictor effect on the pulmonary capillaries which detours the unoxygenated blood away from the alveolar membrane through arteriovenous channels into the left side of the circulation.

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EDITORIAL

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CHORIONIC GONADOTROPIN

CHORIONIC gonadotropin is a hormone of pregnancy. Although hormonal substances similar in behavior and activity may be present in lower mammals, chorionic gonadotropin is essentially a hormone of pregnancy in primates. Among primates, extensive knowledge of this hormonal substance is available only for man.

Chorionic gonadotropin is a glycoprotein. It is produced by the chorionic villi of the placenta and appears in the blood and urine and possibly other body fluids early in pregnancy. It is present throughout pregnancy and disappears shortly after complete delivery of the products of conception. Extensive data constituting "normal curves" on the amount of hormone in the urine and blood are available throughout pregnancy in man. In addition to normal pregnancy, chorionic gonadotropin may be found in certain abnormal states associated or unassociated with pregnancy. Thus, chorionic gonadotropin may be found in exceedingly high amounts in such conditions as hydatidiform mole and chorioepithelioma in the female. In neoplastic disease of the testis, such as chorioepithelioma, and even in tumors histologically categorized as seminoma, this hormone may be present, sometimes also in high amounts. Finally chorionic gonadotropin has been reported in the body fluids of patients with bizarre types of neoplasm, such as certain tumors of the pineal or adrenal and certain extragenital and retroperitoneal types of tumors. It should be emphasized that while virtually every normally pregnant patient will form and excrete chorionic gonadotropin, it does not follow that every patient with the tumors mentioned will form and excrete this substance. Rather the presence of the hormone may depend on the functional capacity of such malignant lesions which may change from time to time during their natural history.

The action of chorionic gonadotropin is implied by the term, gonadotropin. It is a widely effective gonadotropic substance for both the male and female gonad. In certain instances its activity depends on the simultaneous presence of normally functioning and circulating pituitary gonadotropins. In other instances, it has a direct gonadotropic activity per se. Its effects are not restricted to any anatomic unit of the gonads but, depending on the species, may involve any portion of the gonads of both sexes. Finally, it is effective not only in man and other primates but also on the gonads of countless mammals and on representative members of various vertebrate classes.

The only known, normal physiologic action of chorionic gonadotropin is its luteotrophic activity in normal pregnancy of man. Chori-

onic gonadotropin converts the corpus luteum of the menstrual cycle into the corpus luteum of pregnancy, thus prolonging the secretory capacity of the corpus luteum until the placenta can manufacture the high amounts of sex steroids upon which pregnancy depends. This luteotrophic activity is presumably a direct action of the hormone.

Other types of gonadotropic activity may be demonstrated by injection of commercial preparations of this hormone into various species, but these actions are not naturally produced by chorionic gonadotropin since this hormone does not occur normally except in pregnant women. In postnatal man, injection of chorionic gonadotropin not only directly induces differentiation of Leydig cells out of indifferent precursors but induces and maintains the production of male sex hormone. Among lower animals, follicular growth and ovulation are induced by injection of chorionic gonadotropin, probably on the basis of a synergistic action between the administered chorionic gonadotropin and the circulating endogenous pituitary gonadotropins that are present in all normal animals. Injection of chorionic gonadotropin also causes a release of the spermatozoa in lower vertebrates, such as amphibians. It is thus obvious that *indirectly* in combination with pituitary gonadotropins which are present in all normal animals, and *directly* in the absence of any pituitary gonadotropin, as in hypophysectomized animals, and in certain naturally occurring endocrinopathies in man, chorionic gonadotropin may, upon injection, affect the follicular apparatus, the corpus luteum, or the interstitium of the female gonads and the Leydig cell or the seminiferous tubule of the male gonads.

Methods for the qualitative detection and assay of this hormone are legion. Qualitative tests such as pregnancy tests have undergone a considerable evolution since the original Aschheim-Zondek test for pregnancy. This evolution has tended toward greater rapidity in obtaining the result and greater convenience in performing the test. It is evident from the foregoing that there may be many so-called new "tests for pregnancy" still to be discovered, since such tests are limited only by the availability of different animals used to demonstrate the presence of this hormone. Only the more rapid tests will be discussed.

In principle all tests for pregnancy depending on the presence of this hormone should yield similar results. A few basic concepts underlie the performance of pregnancy tests. There appears to be no one animal and no one action of chorionic gonadotropin that is clearly superior to all others. Therefore, the choice of animals rests on such factors as availability, cost, and convenience. In large centers where a rat colony is maintained, the constant supply of genetically uniform animals makes the ovarian hyperemia test attractive and convenient. When only occasional tests are performed, the maintenance of a few frogs for the spermatozoa-releasing action of chorionic gonadotropin may be desirable.

Once the choice of animal and end point is made, the sensitivity of the response must be known. Strictly speaking, tests for pregnancy demonstrate only whether a certain level of chorionic gonadotropin is or is not present. By use of the International standard of chorionic gonadotropin, the amount of hormone in terms of I. U. necessary to induce the chosen response is determined. For ovarian hyperemia this is of the order of 1 I. U. and for various types of frog tests of the order of 10 to 30 I. U. Since urine is the most convenient source for testing, the amount of urine to be injected can easily be determined. Assuming the daily output of urine to be roughly 1,200 cubic centimeters, it is evident that the total excretion of chorionic gonadotropin must be

1,200 I. U. so that 1 cubic centimeter or more of urine may be administered to animals when the sensitivity of the reaction is 1 I. U. Excretion of hormone greater than this value will give positive results for pregnancy; less than this amount, a negative result. It is therefore clear that pregnancy may be present at the time of this test, used as an example, when less than 1,200 I. U. of chorionic gonadotropin are being excreted. It also follows that for end points which require more hormone, correspondingly larger amounts of the urine or concentrates of urine must be administered. Hence the sensitivity in the test limits somewhat the choice of animal and end point, and in general such tests should be of the order of sensitivity so that they may be performed with untreated and unconcentrated urine.

The discriminatory ability of pregnancy tests is the most important single factor, since from previous experience any test to be widely used must be from 90 to 98 per cent accurate. This accuracy is determined not so much by the type of test or the type of animal used but rather by the level of chorionic gonadotropin for which the test under consideration is designed. The amount of hormone excreted changes in direct proportion with duration of pregnancy during the first trimester; hence tests performed some weeks after the missed period would undoubtedly be more accurate than those performed before the missed period. In spite of these generalities, errors apart from purely laboratory errors will and do arise. Occasionally refractory animals or toxic specimens are encountered; occasionally also singular cases are encountered, like that of an obviously pregnant woman who was delivered of a normal child and who during the entire course of her pregnancy, never gave a positive reaction for pregnancy!

As far as specificity of reaction is concerned, no one test for chorionic gonadotropin can be regarded as absolutely specific. To a large extent, all the reactions induced by chorionic gonadotropin may be induced by gonadotropins of other sources, such as the pituitary or endometrium. In clinical practice, specificity is achieved by diluting out pituitary gonadotropins. Hence tests for pregnancy should be designed for levels of chorionic gonadotropin not much lower than 100 to 500 I. U. per day since it is not practical to detect values lower than this and since, even if it were, considerable doubt as to the validity of the test might exist owing to the synergistic activity or contamination with pituitary gonadotropin. It is probably because of this "floor" level that so high a proportion of patients with ectopic pregnancy give negative pregnancy reactions since, for the same period of gestation, less hormone would be presumably formed from a poor than from a normal implantation site.

In addition to the foregoing considerations, it is of course imperative, in order to avoid extraneous error, to use fresh urine, preferably from a morning specimen, and to carry out the test immediately. While, in general, pregnancy tests are not to be classified as emergency laboratory procedures, there is no gain in untoward delay. If the test cannot be carried out immediately, there is no serious danger in storing specimens for at least 1 or 2 weeks, especially if the urine or blood is kept refrigerated. Heating such fluids and severe changes in hydrogen ion concentration will destroy chorionic gonadotropin and will result in negative reactions. Bacterial or fungal growths are undoubtedly deleterious to the integrity of this hormone, but there would seem to be no point in using highly polluted specimens in routine practice.

For quantitative assays of this hormone, any of several recently described methods can be carried out, or in addition, quantitative tests may be constructed on the basis of any

of the responses known for chorionic gonadotropin, provided reasonable care in dilution is maintained and the assay is carried out in comparison with the International standard. Quantitative assays of chorionic gonadotropin are useful in several situations. The diagnosis of hydatid mole and chorioepithelioma is aided by the finding of high titers. However, these conditions are not excluded by the finding of normal titers consistent for that stage of pregnancy, or no titer at all. The presence of chorionic gonadotropin of any magnitude is very helpful in neoplastic conditions of the testis and of intense importance if present in any patient harboring an undetermined malignant lesion, not only for diagnosis, but also in prognosis and as a therapeutic guide. For the male, the significance of any titer of chorionic gonadotropin is underlined when it is remembered that presumably not even 1 I. U. of hormone is naturally present in the normal postnatal male. Recent emphasis on the role of chorionic gonadotropin in pre-eclampsia and diabetic pregnancy, both as to the etiology of the disordered pregnancy and as to its therapeutic management, seems to have been unwarranted in the light of subsequent studies.

A. ALBERT.

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SCOTT OF ABBOTSFORD

ESTHER H. VINCENT, Evanston, Illinois

IN 1771, when Sir Walter Scott was born, the fine old city of Edinburgh was just awakening from the dank placidity of its unhygienic past. People were beginning to wonder if there might not be some connection between their dark, damp basement nurseries and the alarming rate at which their babies died. In the tall, deep buildings little children succumbed with startling rapidity to scarlet fever and diphtheria and to the ever present scourge of smallpox. Susceptibility of young children to "consumption" was realized by few, and yet, when the eminent Scotch chemist, Joseph Black, told the elder Scott that his baby son's nurse was tubercular, the father at once dismissed the girl and gave the care of little Walter to a healthy countrywoman.

The Scotts were descended from the great riding, sporting, and fighting clan of Buccleuch, and Walter senior was the first of his family to live in a town. He was a man of fine presence, conservative and methodical, even ritualistic in the conduct of life. The mother, Anne Rutherford Scott, was a short, "by no means comely" woman, well educated for the time, a comfortable, motherly sort of person, but with an old-fashioned stiffness which kept her from ever leaning back in her chair, even when she was 80.

The first six children of Walter and Anne Scott all died in infancy, but the second six, born after the family had moved from the rather slum-like College Wynd to the more healthful George's Square, all lived to maturity. Walter junior was the fourth of the surviving children, and was a lively little rascal of a baby until he was 18 months old. One night he was especially difficult to handle, toddling wildly about the nursery, until he was finally caught and put to bed. The next morning he was ill with a fever, which his elders thought might be due to teething. On the fourth day, while he was being given a bath, it was noticed that he had lost the use of his right leg.

His maternal grandfather was at once consulted. Dr. John Rutherford had studied abroad, notably in Leyden with Boerhaave, was now head of the Department of Medicine at the University of Edinburgh, and was the man who first introduced the practice of ward teaching there. He and other eminent physicians of the city examined the baby, found no sprain, fracture or dislocation, and could make no satisfactory diagnosis. It was to be another 50 years before poliomyelitis was differentiated. Blistering and other popular remedies were tried in vain. The parents were so frantic that they considered every remedy they heard of, listened to all the old wives' tales, even consulted known quacks. But nothing would cure their little lame boy.

Grandfather Rutherford thought that country air and all possible natural use of the leg might help. So the tiny Walter was sent to Sandy Knowe, his paternal grandfather's little farm. Here he continued to meet strange remedies. His little naked body would be wrapped up in the still warm skin of a freshly killed sheep, and laid on the parlor floor, while Grandfather Scott would try to induce the small cripple to crawl.

A housemaid, unsuspectedly daft, was sent from Edinburgh to look after him. She would carry him up on the crags and there let him lie on the ground. One day she told the housekeeper that sooner or later she intended to murder the baby and bury him in the moss. After this the child was put in care of a shepherd, who would lay him down among the sheep. During a big thunderstorm the shepherd forgot him, and when Aunt Janet ran out to get him, she found him thoroughly enjoying the deluge and shouting, "Bonny! Bonny!" at every flash of lightning.

Young Walter was now in very good health, a winsome, sweet-natured little fellow, surprisingly agile, in spite of his leg. However, his family still hoped for a complete cure, and with this in view, Aunt Janet took him to Bath. For a whole year

the 4 year old boy stoically endured the water regimen of pump room and bath. But he continued to limp. While there he learned to read a little at a dame school and was taken to the theater to see "As You Like It."

Back again at Sandy Knowe, he indulged in vigorous play, clambered up the crags, and galloped his pony over the rough countryside. When he was 8 he took a course of sea-bathing at Prestonpans, which did him no more good than had the sheepskins or the Bath waters. In Edinburgh he was exposed to formal education, but it did not "take" very well, for he was an "incorrigibly idle imp" and much preferred border songs and legends to arithmetic. His slight but obvious lameness did not prevent him from fighting the town boys or from climbing the "kittle nine stanes" on Castle Rock.

When he was 12 he seemed to lose some of his sturdy strength, was thought to be growing too fast, and was sent back to Sandy Knowe for a while. At 14 he had a second serious illness, caused, according to Lockhart, by the "bursting of a blood vessel in the lower bowel." The hemorrhage was considerable, and the lad was confined to his bed and subjected to a kind of open-air treatment. Although the Edinburgh weather was cold and raw that spring, he was covered with but a single blanket. He was bled and blistered until he plaintively said that the remedy was worse than the illness. Talking was prohibited, and his diet was reduced to vegetables. His uncle, Dr. Daniel Rutherford, attended him, and thought his recovery a miracle, as indeed it must have been, considering the treatment. For some time afterward Walter was extremely nervous, starting up at small noises, irritated at trifles, and hesitant in action and speech. Correct diagnosis is impossible at this date, but he might have had ulcerative colitis, although that condition is rare at his age. He was too old for polypus, too young for hemorrhoids, and there was no suggestion of typhoid. His long convalescence gave him ample opportunity to read his favorite romantic tales, to play chess, and, by a special arrangement of mirrors, to watch the soldiers marching by.

Some time later his parents took him to the notorious quack, James Graham, then showing considerable skill in the use of his really fine electrical apparatus. Graham, who used to attend Greyfriars Church in a suit of white and silver, eventually came to grief when a mob tore down his exhibition house, and, after some experiments with earth-bath therapy, he slowly starved to death. Needless to say, his electric treatments had no effect on Walter.

As a young man, Scott was tall and muscular, with a figure that was both powerful and graceful. His high, almost conical head towered over the heads of others like a mountain peak. His head was not exactly abnormal, but it was not a common type. Craniometrically, though not clinically, he was megacephalic. Some medical men have attributed his oddly shaped skull to the fact that, while growing, his head was deprived of the upright position for long periods when he was ill. He was far from handsome, for he had a longish upper lip and a not too vigorous chin. Nevertheless he was attractive, owing to a certain mobility of expression. His light blue eyes were bright, his teeth white and regular, his hair and bushy eyebrows a rich nut-brown, his smile was delightful, and he was a charming companion. It was a proud day when he found out that a pretty girl really liked to sit out with him the quadrille that he could not dance.

He had no ear for music, and his sense of smell was hardly more delicate, but he had a keen eye, with a remarkable perception of color. His fascination for animals, children, servants, and laborers was magical.

An early disappointment in love saddened him and probably restrained his youthful ardors. But in 1797, while visiting the English Lakes, he saw a beautiful young woman, Charlotte Mary Charpentier (or Carpenter), daughter of a French refugee, whom he sought out and eventually married. She proved to be a pleasant, if not a stimulating companion, and gave him four children, two girls and two boys.

Scott was early apprenticed to his father, a writer (lawyer) to the Signet, and easily attained regular business habits. He added to his pocket money by copying legal documents, and thus achieved that methodical industry that so characterized his later life. Aspiring to the bar, he attended civil law classes, and at length produced as his thesis, "On the Disposal of the Dead Bodies of Criminals." After his father's death in 1799, he became deputy sheriff of Selkirkshire, and also got a clerkship, with duties so light that he was able to give much of his time to his budding authorship.

His military enthusiasm was so great that if it had not been for his lameness, he would probably have become a soldier. As it was, he helped raise a body of volunteer cavalry in 1797, and as quartermaster attended early morning drills before going about his legal business. In 1805, when there was a false alarm of Napoleonic invasion, he "did a Paul Revere," riding 100 miles in a single day.

During these years he was in robust health, and played and worked with amazing vigor. Occasionally he would have nervous headaches, cured by attending to his physician, who told him to give up study and writing late at night. Instead he got up at 5 in the morning. He spent many afternoons in the open air, riding and walking and playing games. He enjoyed every kind of weather, and, even during his later years of ill-health, could not be kept indoors by rain or snow. He had his share of trivial ailments, colds and the like, and acquired the habit of treating a sore throat by sponging his throat, chest, and shoulders every morning with the coldest of water. From youth to age he was reluctant to resort to physicians or drugs.

In the winter of 1816–1817 he began to suffer from the third serious illness of his life. Gallstone colic was hereditary in his family, but dietary indiscretions may have contributed to Scott's biliary calculi. He was ever a moderate drinker for his day, but was too good a trencherman, eating Gargantuan breakfasts of roast beef, pasties, cold sheepshead, and chunks of the huge brown loaf of Scotch bread. His wine drinking he limited to claret and champagne, but he liked many whiskey toddies. Port he considered a physic, and never willingly swallowed more than one glass at a time. As his poetry and novel writing increased, his outdoor exercise decreased, and in winter he got very little of it, although he frequently dined out sumptuously.

Whatever the cause, he suffered intermittently for more than 2 years from violent attacks of biliary colic. He never seems to have considered surgical aid, although these attacks very nearly cost him his life. In fact, he never entirely recovered from their effects. He was bled and blistered until he thought he would have neither skin nor blood left. "Cramp setting fire to its lodging" is his graphic description of the onset of the acute cholecystitis. The attacks became more frequent and severe, reaching a climax in the spring of 1819.

At this time he was alone at Abbotsford with his elder daughter, Sophia, and during the course of the 10 day attack, Scott was completely exhausted by the violence of the pain and the spasmodic contraction of the stomach muscles. The heavy fire of medical artillery directed against him was not less prostrating. There was the usual bleeding and blistering, the administration of ipecacuanha and calomel without ceasing. Laudanum and opium were given for relief of pain, but his groans of agony could be heard outside the house. After a night of such suffering, he would get up early in the morning and ride 20 miles on his horse.

These repeated attacks produced a sad change in his appearance. His hair turned white, his skin turned yellow, his slight obesity melted away into a gaunt, haggard emaciation. Beer and ale, pastry and fruit were eliminated from his diet. For pain he tried hot baths and hot salt bags, but nothing really relieved him except large amounts of opium, which did not agree with him, and had to be counteracted with other drugs, thus setting up a "disagreeable seesaw," as he termed it.

From his friends he received enough advice to fill a pharmacopoeia. Watering places were suggested, but he did not like watering places. His Highland piper, John Bruce, spent one whole Sunday selecting 12 stones from 12 south running streams and brought them to Scott to sleep on, as a sure cure. Scott got out of the situation by asserting that the charm would not work unless the stones were wrapped in the petticoat of a widow who had never desired to remarry. Along with all of this, Scott's left leg swelled up and became inflamed. The muscles failed him, and he had to be carried about.

One day when a gallstone attack occurred, Scott took a large dose of calomel on his own initiative, and when the pain almost immediately subsided, he thought he had cured himself, especially when it so happened that he never again had a bad attack, although he sometimes complained of biliousness. When Sophia had a similar attack shortly after childbirth, Scott gave her calomel, believing it to be a specific for the disease.

During his suffering, he carried on his writing with stoical courage. During his 2 years of agony, he wrote the whole of *The Bride of Lammermoor*, and parts of *Ivanhoe* and of *Rob Roy*, but he could never remember what he had written. He always said that *Rob Roy* smelled of cramp.

In 1820 Scott went to London to receive a baronetcy at the hands of George IV, and in the same year was induced to accept the presidency of the Royal Society of Scotland, although he knew little of science. He was able to make friends of the scientific members and to add charm, at least, to their meetings. Other clubs and societies, too, added to his social activities. In 1821 he attended the coronation of George IV, and in 1822 was master of ceremonies at the visit of the King to Edinburgh. Such was his enthusiasm for the somewhat unattractive monarch, that he begged for the glass out of which the King had drunk his health, and in a moment of mental aberration sat down upon it, luckily injuring only the glass. As a result of fatigue and anxiety over the success of the royal visit, Sir Walter developed a curious skin disease, "a very inconvenient and

nasty eruption" which spotted his legs and arms for years. Then in December, 1825, he had a bad attack of renal colic with violent pain in the right kidney, but this, mercifully, was a solitary episode.

About the same time, when he was 54, he had some kind of urinary trouble, but did not say enough about it to give any clue as to its exact nature. It is known, however, that he was alarmed, and decided then and there that he would probably die in a few years. "Square the odds, and goodnight, Sir Walter, about 60."

All his life he experienced intermittent attacks of a nervous disturbance, which he sometimes referred to as the "morbus eruditorum" and sometimes as the "black dog." In his *Journal* he wrote that it was characterized by heart tremor, baseless fear, and lassitude. He further stated that he had it "less now than when young."

During the winter of 1826–1827 he complained of successive attacks of severe "rheumatism," probably fibrositis, which he thought he got from sleeping between wet sheets at a French inn. Because of this he could not exercise, and so he thought it contributed to the final breakdown of his health.

Meanwhile financial ruin stared him in the face. In 1826 Sir Walter's fortune vanished when his publishers went bankrupt. His affairs were so closely bound up with theirs that he felt himself personally responsible for the huge debt. Since he had not saved any money, having spent his substance on land and hospitality and on helping others, the only way he could repay his creditors was by a crushing schedule of constant writing. The minute he finished one novel he had to begin another. Added to the economic distress and the blow to his pride, came family worries. In May of that same year his wife died and later, his little grandson, John Hugh Lockhart. Of his wife's illness, he wrote: "The complaint is of water in her chest, and the remedy is of foxglove, which seems a cure rather worse than most diseases, yet she sustains both disease and the remedy to the surprise of medical persons."

The first mention of possible hypertension appeared in one of his letters written as far back as November, 1822. He then noted symptoms of a "thickness of blood and depression," which may have concealed a slight stroke. Later he wrote of a throbbing at the heart, nervousness, insomnia, precordial pain, headaches, some mental confusion and dizziness. Since his father, mother, and brother had all died of apoplexy, there may have been a hereditary tendency to arteriosclerosis. In June, 1829, he had a vague attack, but after some weeks of headaches, nervous irritation, and copious cupping, he grew fairly well until the following February when he had his first definite stroke.

On February 15, 1830, he returned from Parliament House about 2:00 in the afternoon to find an old acquaintance, Miss Young, of Hawick, waiting to show him some memoirs of her father, which she wanted Sir Walter to edit for publishing. They sat and talked together for about half an hour. Scott then rose, but immediately sat down again with some slight convulsion of the face. After a few minutes he rose and staggered to the drawing room where his daughter Anne and Violet Lockhart were sitting. He was unable to speak and remained so until a surgeon came in about 10 minutes and bled him.

This attack so frightened him that he gave up smoking for a time. His family suggested that he have a medical student as his secretary, since at Abbotsford, to which he now retired, there was no physician near by. But Scott would have none of the medical student, and so the surgeon, Mr. James Clarkson, privately instructed a servant in the use of the lancet. Another, but slighter, stroke came in November of the same year, and now he had no further doubts as to the nature of his illness.

Unlike Samuel Johnson, Scott was never afraid of death. Even in the colicky year of 1819, when he himself thought that he was dying and said farewell to his wife and children, he squarely faced his expected death and wanted to face it alone. But he did dread mental deterioration, having witnessed it in his father and in other members of his family, who lingered on for months and months, shattered in both mind and body by apoplexy. However he bore the realization of his probable future with his usual cheerful fortitude.

A third attack in April 1831 was more severe. There was now an obvious distortion of the cheek muscles, some hesitation in speech, and some signs of mental impairment. He would gaily begin a story, but would falter and be unable to finish it. In this condition he tried to take part in the May electioneering, to which his strong sense of duty called him, as well as his position as sheriff. A born Tory, he was opposed to the popular reforms of the day, and, unfortunately, his personal popularity did not prevent him from being mobbed by fanatical radicals at Jedburgh. The brutal cry of "Burke Sir Walter," hurt him badly.

By July he felt well enough to take a short driving tour with his son-in-law, Lockhart, and in September he was induced by his friends to seek further improvement on the continent. By this time he was under the illusion that he had paid all his debts and could stop driving himself to write.

In London he was seen by Dr. Robert Ferguson, Sir Henry Halford, and Dr. Holland. During their absence from the room, Sir Walter shrewdly placed his chair in a dark corner facing the door, so that he might more easily read their faces when they returned from consultation. All three concurred in a diagnosis of incipient brain disease, but thought that if he ceased working, the disease might be arrested.

He visited Malta, Naples, and Rome, did some sightseeing and also did some writing, probably out of habit. The party returned to Britain via the Rhine, and on the way Scott had another attack, relieved by his servant's lancet. On arriving in London on June 13, he stayed at a hotel in Jermyn Street, again seeing his three doctors. Still retaining his personal dignity, he was nevertheless in a sort of waking dream, and did not arouse himself on the journey home until he came in sight of Abottsford. Then he became so excited that he was held in the carriage with difficulty. At Abbotsford, with only one clear interval of consciousness, he lingered on for 2 months, dying early in the afternoon of September 21, a glorious autumn day, with the Tweed lapping happily over its pebbles, and the sunlight gold on the Eilden Hills.

An autopsy, limited to the head, was carried out by the country physician, Mr. Clarkson, in the presence of Dr. Adolphus Ross of Edinburgh.

> On removing the upper part of the cranium, the vessels on the surface of the brain appeared slightly turgid, and on cutting into the brain the cineritious substance was found of a darker hue than natural and a greater than usual quantity of serum in the ventricles. Excepting these appearances, the right hemisphere seemed in a healthy state, but in the left, in the choroid plexus, three distinct though small hydatids were found; and on reaching the corpus striatum it was discovered diseased—a considerable portion of it being in a state of ramollissement. The blood-vessels were in a healthy state. The brain was not large—and the cranium thinner than it is usually found to be.

Since both Scott and Byron were lame, comparison seems natural. Scott was one of a large family of steady, respectable, middle class people, calm and placid, gentle and kind. Byron was the only son of an aristocratic, neurotic parentage. Unexpectedly raised from near poverty to high life and instantaneous poetic success, he finally sank into all sorts of excesses through lack of self discipline and through overcompensation for his clubfoot.

Scott began to wear a brace shortly after his first apoplectic attack, was actually proud of it, and wore it all the rest of his life. Byron had one surgical boot made when he was 11, and another when he was 18. There may have been others, but these two, both for the right foot, have been preserved. Another boot was worn over the corrective boot. It is the irony of fate that the corrective appliance of Scott, who took his lameness as pleasantly as possible, has completely disappeared, while that of Byron, who would have moved heaven and earth to conceal his deformity, has been preserved. It may be noted that Scott sturdily defended Byron when that unhappy poet's reputation for moral turpitude threatened to undermine his reputation for poetry.

Scott's experience with doctors did not especially endear the profession to him, although he paid personal tribute of gratitude and admiration to Clarkson. In none of his novels has he given us a full study of a physician, although there are a goodly number of them among his minor characters. He writes of his own illnesses with considerable humor and endured the odd remedies inflicted upon him with patience and faith. But he sums up the profession thus: "A doctor is like Ajax—give him light and he may make battle with a disease; but, no disparagement to the Esculapian art, they are bad guessers."

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3. Hutchison, R. The medical history of Sir Walter Scott. Edinburgh M. J., 1932, 39: 461–485.
4. Hutton, R. H. Sir Walter Scott. New York: Harper, 1879.
5. M'Neil, C. Sir Walter Scott and *Res Medica*. Edinburgh M. J., 1932, 39: 486–496.
6. Stephen, L. Sir Walter Scott. Dict. Nat. Biog., London, Smith, Elder & Co., 1897, 51: 80–112.

REVIEWS OF NEW BOOKS

THE delightful volume *Medical Biographies*[1] combines with unusual success biography and medical science. It is a series of sketches written in enjoyable prose about the great and near-great of the past with respect to their frailities, strength, and illnesses and can be read with interest both by lay-readers and members of the medical profession. It is especially interesting to review the descriptions and diagnoses of their illnesses in the light of modern medical knowledge. The author has attempted to illuminate the dark corners of medical biography in a few instances of extreme interest.

Throughout the book, an effort has been made to avoid medical terms without sacrificing essential detail. Although the appeal is directed essentially to the layman, it was with great interest that these pages were read by the reviewer.

The research which the author has carried out, especially in analyzing the fatal illnesses of those famous persons of remote times, must necessarily be considerable. The accuracy of his detailed research and his deductions must be commended. The medical history of Napoleon, Charlemagne, William the Conqueror, Benvenuto Cellini, Sir Isaac Newton, Charles Darwin, and Nancy Hanks Lincoln, to name a few, are examined in a most engaging style. The author has the ability to be brief without becoming telegraphic in style.

It is my feeling that this volume should find its rightful place on the bookshelves of most American practitioners. A glance into the past which this book provides is not only enjoyable reading, but is also of great interest with respect to modern medical practice. ORVILLE F. GRIMES.

THE monograph *Die Fruehdiagnose des Uteruscarcinoms*[2] presents data to support adequately the contention that the diagnosis of early carcinoma is no longer experimental. The incidence of superficial preinvasive lesions per 100 cases of carcinoma of the cervix rose from 4.4 to 24.2 per cent with the use of biochemical, colposcopic, and cytologic adjuncts to histologic diagnosis.

The biochemical procedures are too difficult for general use and are restricted to tests by special laboratories on the few cases otherwise not well defined. However, colposcopy and vaginal cytology techniques are essential and adaptable to the practicing physician's search for early uterine cancer.

The author's experience with cytology parallels that of investigators in this country. He uses the technique to detect the hidden and asymptomatic lesions. He considers colposcopy, although generally ignored in the United States, essential to precise selection of biopsy sites in grossly altered epithelia.

A wealth of material on early genital cancer is presented and well illustrated. FRANK M. MAHER.

THE sixth edition of *A Textbook of Gynæcological Surgery*[3] by Victor Bonney is, like its predecessors, an excellent exposition of gynecological surgical precepts and techniques. It again fulfills the hopes expressed by Comyns Berkeley and the author in the first edition published in 1911, i.e., that it would be of service both to those primarily interested in gynecology as well as those who, of necessity, are called upon to perform gynecological operations.

The general arrangement of the text follows that of previous editions. It is well organized and easily readable. Six hundred and eleven of the 628 illustrations are pen and ink drawings by the author.

The present edition gives in detail the author's indications for gynecological operations, his preoperative preparations, his operative techniques, dangers to be avoided in pelvic surgery, his postoperative treatment, management of possible postoperative complications and the results of gynecological procedures in hospitals with which he has been associated. Descriptions of pelvic exenteration and the radical operation for carcinoma of the vulva have been incorporated in this edition.

The physician who has been trained in the United States will find it an interesting and valuable presentation of gynecological principles and procedures by an eminent British gynecologist who has made many noteworthy contributions to the advancement of his specialty. JOHN W. HUFFMAN.

THE evolution of congenital heart disease from an autopsy table curiosity to a vitally important clinical entity has brought with it a new requirement for the author of a book on this subject. A vast clinical experience is necessary, for from it comes the perspective and clarity needed in a relatively new and rapidly developing field.

It would seem that without this experience available to him, the author has relied for much of his material on the current literature, with some of the disadvantages that that implies.

Congenital Anomalies of the Heart and Great Vessels[4] is a rather extensive review of the recent work

[1] MEDICAL BIOGRAPHIES; THE AILMENTS OF THIRTY-THREE FAMOUS PERSONS. By Philip Marshall Dale, M.D. 1st ed. Norman, Okla.: University of Oklahoma Press, 1952.

[2] DIE FRUEHDIAGNOSE DES UTERUSCARCINOMS; HISTOLOGIE, KOLPOSKOPIE, CYTOLOGIE, BIOCHEMISCHE METHODEN. By Prof. Dr. Med. Hans Limburg. Stuttgart: Georg Thieme, 1952.

[3] A TEXTBOOK OF GYNAECOLOGICAL SURGERY. By Victor Bonney, M.S., M.D., B.Sc. Lond., F.R.C.S. Eng., Hon. F.R.A.C.S., Hon. F.R.C.O.G., M.R.C.P. Lond. 6th ed. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1953.

[4] CONGENITAL ANOMALIES OF THE HEART AND GREAT VESSELS. By Maurice A. Schnitker, B.S., M.D., F.A.C.P. New York: Oxford University Press, 1952.

on congenital heart disease, not all of it important, but contains bibliographies that will be of value to the student. To the physician, however, the crux of the problem in congenital heart disease is the clinical diagnosis and the selection of the surgical cases, and unfortunately, he will not readily find a well organized, clearly described method in this book.

ROBERT A. MILLER.

THE third edition of *The Pharmacology of Anesthetic Drugs*[1] is one of the most useful books in the field of anesthesiology. The general plan remains the same as in previous editions. The addition of recently acquired pharmacological data, elaboration of existing subject matter, and more detailed description of clinical material has doubled the page capacity. However, the use of a lighter weight paper has permitted little increase in size of the volume.

The format is attractive. The many diagrams are similar to those previously used and the context is in the same condensed, telegraphic style. The arrangement of topics has been changed somewhat and charts showing classes of drugs have been added. Of particular interest is the inclusion of material on muscle relaxants, trichlorethylene, synthetic alkaloids, and drugs acting on the autonomic nervous system. New sections deal with the effects of depressant drugs on cells and tissues, with the relation of physical and chemical behavior to depressant effects on the cell, and with detoxification of depressant drugs. Topics which have undergone extensive revision include barbiturates, local agents, inhalation drugs, and factors influencing absorption and elimination of volatile drugs as well as complications and accidents and postanesthetic sequelae.

The objective of acquainting the anesthetist with pertinent facts relating to drugs in current use has been attained. The book will be of interest to students and instructors of anesthesiology and will be useful as a reference for data relating to anesthetic drugs.

MARY F. POE.

THE second edition of *Tuberculosis of Bone and Joint*[2], by E. W. Somerville and the late G. R. Girdlestone, brings up to date the present British concepts of skeletal tuberculosis. The book may well serve as a memorial to the late Professor Girdlestone, who devoted a lifetime of work and thought and contributed so much to the understanding as well as to the management of tuberculosis of bone and joint.

From the standpoint of the systemic nature of the disease, pathology, differential diagnosis, and stress of the need for individualization of each instance of tuberculosis of bone and joint, orthopedic surgeons in America have no quarrel and little reason to differ with the authors. Disagreement will arise, however, on the basis of the de-emphasis of bacteriologic examination as evident in this work. Although the worth of clinical, roentgenologic and histologic methods of diagnosis is not to be underestimated, most American authorities feel that the *sine qua non* in the diagnosis of tuberculosis rests with the bacteriologist. By modern cultural methods the bacteriologist can, by study of an adequate sample of debris or pus from a granulomatous lesion, identify Mycobacterium tuberculosis in almost all cases of tuberculosis. Moreover, in the majority of instances of skeletal tuberculosis, an adequate sample of material for bacteriologic study can be removed by needle aspiration; never have we seen harm to the patient result from such a procedure. Only by culture for acid-fast organisms and by inoculation of guinea pigs with suspected material can tuberculosis be positively distinguished from other granulomatous lesions. Only by these means is a sound basis for proper therapy provided.

To expatiate: In America it has been established generally that the prolonged recumbent therapy prior to operation as advocated by the authors and other British authorities in the treatment of skeletal tuberculosis, and especially in Pott's disease, usually is not necessary.

Arthrodesis of a tuberculous knee in a child may be the treatment of choice, provided care is taken to preserve the epiphysis. Such a procedure is condemned by the authors. On the other hand, it is possible that in the United States in the past the tendency has been to sacrifice motion in a tuberculous joint, even though the actual site of the disease apparently was only synovial. Since the advent of chemotherapeutic and antibiotic drugs, a more conservative approach is being adopted in instances of early tuberculosis of a joint.

The authors discuss a rational timing and a method of decompression in the treatment of Pott's paraplegia. This should be carried out more frequently in America.

This book is stimulating, educational, well written, and illustrative. It is of special value in promoting an understanding of the pathogenesis and differential diagnosis of skeletal tuberculosis. Certainly, the authors have had a vast experience with the subject, and their methods of management in the main are tried and true. Speculation could be raised as to whether orthopedic surgery in America has been too radical and that in England too conservative. As time and further study progress on both sides of the Atlantic, this question should be settled.

PAUL R. LIPSCOMB.

THIS beautifully illustrated volume of 900 pages, *Lehrbuch der roentgenologischen Differentialdiagnostik*[3] is devoted, as its title indicates, to diseases of the thorax. More than one-half of the volume, 545 pages, is devoted to the lungs and

[1] THE PHARMACOLOGY OF ANESTHETIC DRUGS; A SYLLABUS FOR STUDENTS AND CLINICIANS. By John Adriani, M.D. 3rd ed. Springfield, Ill.: Charles C Thomas, 1952.

[2] TUBERCULOSIS OF BONE AND JOINT. By G. R. Girdlestone and E. W. Somerville, M.B., F.R.C.S.(Ed.). 2nd ed. London, New York, Toronto: Oxford University Press, 1952.

[3] LEHRBUCH DER ROENTGENOLOGISCHEN DIFFERENTIALDIAGNOSTIK. ERKRANKUNGEN DER BRUSTORGANE. By Werner Teschendorf. Vol. 1. Stuttgart: Georg Thieme, 1952.

mediastinum, 350 pages to the heart, and the last 100 pages to the esophagus and diaphragm.

An outstanding feature is the excellence and clarity of the 1,030 illustrations. They are beautifully reproduced and consistent with the high standards we have come to expect of German publications. They give point to the author's quotation from Goethe in his preface, "The most difficult thing of all is to see what lies before your eyes."

In the first section, on the lungs and mediastinum, the author has chosen to classify his material by the character of the roentgen picture—conditions with involvement of one-half of the thorax, conditions causing dense shadows of part of the lung, shadows within the pleural space, shadows within single lobes, interlobar and middle lobe shadows, and going on to conditions showing diffuse involvement, striated shadows, cavity formation, and air-containing spaces. A helpful feature is the frequent presentation of different stages of the disease process in the same patient. The concluding chapters of the section upon the lung are devoted to the bronchi, the normal lung, the hilus, and mediastinum.

In the section upon the heart are included a brief discussion of angiocardiography and a well illustrated discussion of congenital abnormalities with helpful illustrative diagrams. Throughout the section on the heart the roentgenograms of the heart are frequently accompanied by electrocardiograms of the case illustrated, and in a separate chapter of 54 pages, entitled "Electrocardiographic Changes and the Roentgen Picture," the author correlates the electrocardiographic changes with the roentgen picture in practically every condition with abnormal electrocardiographic findings. In the concluding chapters on the heart are included chapters on the coronary arteries and the differential diagnosis of diseases of the aorta.

Well illustrated sections on diseases of the esophagus and the differential diagnosis of the changes in the diaphragm seen in the roentgenogram conclude the volume.

Altogether this volume constitutes an admirable and comprehensive encyclopedia of the roentgenologic findings of practically every disease process including the thoracic contents. SUMNER L. KOCH.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

OSTEOSKLEROSE UND KNOCHENMARKFIBROSE. By Rudolf Stodtmeister, Stefan Sandkühler, and Albert Laur. Stuttgart: Georg Thieme, 1953.

1953 MEDICAL PROGRESS; a REVIEW OF MEDICAL ADVANCES DURING 1952. Edited by Morris Fishbein, M.D. New York, Toronto: The Blakiston Co., 1953.

SURGERY OF THE OESOPHAGUS. By R. H. Franklin. M.B., B.S., F.R.C.S. Baltimore: The Williams & Wilkins Co., 1952.

THE MANAGEMENT OF ABDOMINAL OPERATIONS. Edited by Rodney Maingot, F.R.C.S. New York: The MacMillan Co., 1953.

KLINISCHE FEHLDIAGNOSEN. By Prof. Dr. M. Bürger. Stuttgart: Georg Thieme, 1953.

CHIRURGIE PLASTIQUE CUTANÉE; PRATIQUE COURANTE. By J. Francillon and P. Truchet. With the collaboration of G. Fournie, A. Gaté, and M. Terrel. Paris: G. Doin & Cie, 1953.

KOLPOFOTOGRAMME ZUR EINFÜHRUNG IN DIE KOLPOSKOPIE. By Dr. med. Robert Ganse. Vol. 1. Berlin: Akademie, Verlag, 1953.

DOCTOR IN THE HOUSE. By Richard Gordon. New York: Harcourt, Brace & Co., 1953.

LA PLASTIE MAMMAIRE PAR LA MÉTHODE OBLIQUE. By Hélène Marc. Illustrated by Jean Castaing. Paris: G. Doin & Cie, 1952.

OCCLUSION INTESTINALE; CLINIQUE CHIRURGICALE DE L'HOSPITAL COCHIN. Edited by Jean Quénu. By various authors. Paris: G. Doin et Cie, 1953.

HYPNOSIS IN MODERN MEDICINE. Edited by Jerome M. Schneck, M.D. Springfield, Ill.: Charles C Thomas, 1953.

ON BURNS. Compiled and edited by Nathan A. Womack, M.D. Springfield, Ill.: Charles C Thomas, 1953.

CURRENT THERAPY 1953; LATEST APPROVED METHODS OF TREATMENT FOR THE PRACTICING PHYSICIAN. Edited by Howard F. Conn, M.D. Philadelphia, London: W. B. Saunders Co., 1953.

NEUE DEUTSCHE CHIRURGIE. Founded by P. v. Bruns. Vol. 58. SPORTSCHÄDEN UND SPORTVERLETZUNGEN. By Prof. Dr. Burghard Breitner. 2nd rev. ed. Stuttgart: Ferdinand Enke, Verlag, 1953.

ATLANTE DI CITODIAGNOSTICA DEL CARCINOMA DELL' UTERO. By Dr. Enzo Martella. Preface by Prof. G. Tesauro. Naples: Casa Editrice V. Idelson, 1952.

DIE BEHANDLUNG DER KNOCHEN- UND GELENKTUBERKULOSE. By Doz. Dr. Heinz May with collaboration by Dr. Wilhelm Lang, Dr. Richard May, and Franz Novotny. Stuttgart: Ferdinand Enke, Verlag, 1953.

PLASTIC SURGERY AT THE NEW YORK HOSPITAL ONE HUNDRED YEARS AGO WITH BIOGRAPHICAL NOTES ON GURDON BUCK. By Herbert Conway, M.D., and Richard B. Stark, M.D. Forewords by John Hay Whitney, Stanhope Bayne-Jones, M.D., and Frank Glenn, M.D. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1953.

DAS ULKUS DES MAGENS UND ZWÖLFFINGERDARMS ALS PROBLEM EINES SCHUTZSTOFFMANGELS. By Dr. H. Ramb. Stuttgart: Georg Thieme, 1953.